

REVIEW ARTICLE

## Do mast cells link obesity and asthma?

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### Abstract

Asthma is a chronic inflammatory disease of the lungs. Both the number of cases and severity of asthma have been increasing without a clear explanation. Recent evidence suggests that obesity, which has also been increasing alarmingly, may worsen or precipitate asthma, but there is little evidence of how obesity may contribute to lung inflammation. We propose that mast cells are involved in both asthma and obesity by being the target and source of adipocytokines, 'alarmins' such as interleukin-9 (IL-9) and interleukin-33 (IL-33), and stress molecules including corticotropin-releasing hormone (CRH) and neurotensin (NT), secreted in response to the metabolic burden. In particular, CRH and NT have synergistic effects on mast cell secretion of vascular endothelial growth factor (VEGF). IL-33 augments VEGF release induced by substance P (SP) and tumor necrosis factor (TNF) release induced by NT. Both IL-9 and IL-33 also promote lung mast cell infiltration and augment allergic inflammation. These molecules are also expressed in human mast cells leading to autocrine effects. Obese patients are also less sensitive to glucocorticoids and bronchodilators. Development of effective mast cell inhibitors may be a novel approach for the management of both asthma and obesity. Certain flavonoid combinations may be a promising new treatment approach.

The prevalence of both asthma (1) and obesity (2) has been increasing steadily over the last 20 years. A meta-analysis of prospective epidemiological studies indicated that obesity and asthma co-exist in many patients (3). Moreover, triggers of severe asthma are still not well understood (4,5). Obesity has been linked to inflammation (6,7). White adipose tissue (WAT) has been implicated in several pathophysiologic mechanisms: (i) metabolism of fatty acids; (ii) production of adipocytokines, including C-reactive protein (CRP), IL-6, IL-9 and IL-18 (8); (iii) synthesis of angiotensinogen, adiponectin, resistin and leptin (9), as well as (iv) insulin resistance. Macrophages (10) and mast cells (11) are increased in obese

WAT compared with lean tissue. Saturated fatty acids can stimulate toll-like receptors (TLRs) (12) and lead to cardio-metabolic deregulation (13).

Obesity is a major risk factor for type 2 diabetes, possibly due to the inflammatory response that could alter adipose tissue function (7), thus leading to insulin resistance (14), and worsen asthma control (5,15–18). One study concluded that the association between obesity and asthma (atopic and nonatopic) was independent of insulin resistance and socio-demographic factors (19).

Adipocytokines have been associated with allergic inflammation and mast cells (4,20,21). Mast cells are involved in

asthma pathogenesis (22,23) and in the metabolic syndrome (23,24). Advanced glycation end products (AGEs) that accumulate in diabetes and obesity can also activate mast cells (25).

### Obesity as an inflammatory state

Obesity is now considered a chronic inflammatory state involving cytokine release from adipocytes (6,26). WAT secretes a number of hormones, such as adiponectin and leptin. Leptin is mainly secreted by adipocytes and is markedly increased in obesity; it regulates body weight but also regulates various immune and inflammatory processes (27).

One study showed that leptin levels in children correlate positively with the basal metabolic index (BMI), airway reactivity and total immunoglobulin E (IgE) (28), as well as with exercise-induced bronchoconstriction (29). Higher serum leptin was reported in children with asthma, but did not have a direct effect on the airways (30). In fact, leptin was independent of obesity in mice (31). One review of such studies concluded that leptin does not have a significant direct role in the association between obesity and asthma (32). Instead, leptin may be affecting lung function through mast cells, especially because both leptin and leptin receptors are expressed by human mast cells (33).

Decreased adiponectin release from adipocytes, observed in obesity, is associated with insulin resistance and hyperinsulinemia (34). Weight loss and adipocyte mass reduction result in a decrease in pro-inflammatory adipokine production and an increase in circulating adiponectin.

Visfatin is an insulin-mimicking adipokine and is significantly increased in subjects diagnosed with obesity, type 2 diabetes, and the metabolic syndrome (35). A strong correlation was found between visfatin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) expression in adipose tissue and peripheral blood mononuclear cells (36).

Resistin is an adipocytokine with a controversial role in the pathogenesis of obesity-mediated insulin resistance and type 2 diabetes, but acts like a pro-inflammatory cytokine (37) and also leads to secretion of other pro-inflammatory cytokines (38). Patients with asthma were found to have higher levels of resistin, and resistin levels were increased with disease severity (39). Adipose tissue of obese individuals also releases IL-6 and Regulated on Activation Normal T Cell Expressed and Secreted (RANTES) (40), which is a potent mast cell chemoattractant (41).

### Obesity and asthma

Numerous studies suggest that obesity and adipocytokines (32,42) are risk factors for asthma (3,43,44). Obese patients appear to have abnormal levels of serum and airway adipocytokines (45). In contrast to leptin, adiponectin has anti-inflammatory properties. In children, adiponectin negatively correlates with BMI (46), and lower adiponectin levels in cord blood are associated with increased risk of developing wheezing disorders within the first 2 years of life (47). It was also shown that adiponectin levels in asthmatic children

negatively correlate with exercise-induced bronchoconstriction (29). A recent study also reported that childhood obesity is associated with higher risk of asthma control and severity (48). Interestingly, a recent study of 3-year-old children with asthma reported a positive relationship between obesity and asthma, but only in boys and not in girls (49). In contrast, a study of 411 adults demonstrated, after adjusting for body mass, that high serum adiponectin was strongly associated with asthma in men than in women (50). Nevertheless, a recent study of 1450 women reported that low adiponectin levels at year = 15 predicted significantly higher risk for asthma at year = 20, especially in smokers (51).

Obesity also worsens airway inflammation (52) as obese asthma patients are in need of increased inhaled steroids to achieve good asthma control (48). Overweight children had increased hospital admissions for asthma (53) and required longer and higher doses of steroids to recover than those of normal weight (54). There was also a correlation between obesity, asthma severity and exacerbations, as well as increased serum IgE (55).

Westernized diet, such as low antioxidant intake and high saturated fat intake, contributes to an elevated inflammatory state in asthma due to activation of the innate immune response (56). Levels of 8-isoprostane and other markers of oxidative stress are increased both in the blood (57) and in the lungs (58) of obese *vs* lean patients with asthma. Moreover, oxidized lipoproteins can activate mast cells (59).

### Mast cells and lung inflammation

Mast cells are necessary for the development of allergic reactions (60), through crosslinking of their surface high-affinity receptors for IgE (Fc $\epsilon$ RI), leading to degranulation and the release of vasoactive, pro-inflammatory, and nociceptive mediators, such as arachidonic acid metabolites, histamine, cytokines, and proteolytic enzymes (60,61). Many of these molecules are known to participate in asthma (62).

Mast cells can also be activated by various immune and environmental triggers. These include proteases, such as chymase and tryptase, stem cell factor (SCF) and TNF, as well as TLR ligands (63,64) and immunoglobulin light chains that have been implicated in allergic asthma (65).

IL-33 (66) induces mast cell production of IL-13 (67) and promotes mast cell survival (67). Mast cells have been considered 'sensors of cell injury' through IL-33 (68). IL-33 is produced by mast cells and regulates airway allergic inflammation (69). Moreover, IL-33 connects mast cells, dendritic cells, and Th2 cells in an animal model of asthma (70). In addition to IL-33, IL-9 is involved in allergic inflammation (71) and permits antigen-induced mast cell infiltration of the lungs (72).

Many triggers may participate in lung inflammation together with neuropeptides secreted locally that stimulate mast cells. For instance, we showed that corticotropin-releasing hormone (CRH) and NT act synergistically to increase vascular permeability (73). We further showed that IL-33 augments human mast cell release of vascular endothelial growth factor (VEGF) in response to substance P (SP) (74).

Mast cells are adjacent to blood vessels in the lamina propria of airway mucosa (20). In patients with asthma, mast cells also migrate into airway epithelium (62,75) and airway smooth muscle (76). This anatomical proximity to key structures involved in asthma and *in vitro* evidence for direct interaction between mast cells and airway smooth muscle cells (SMC) (77) suggest that mast cells play a significant role in the pathophysiology of asthma (75,78) through the release of multiple mediators in response to both immunoglobulin E (IgE) (20) and monomeric IgE (79).

After activation, mast cells secrete histamine, prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), and leukotriene C<sub>4</sub> (LTC<sub>4</sub>), which induce bronchoconstriction, mucus secretion, and mucosal edema, thus contributing to the acute symptoms observed in asthma (75,78,80). Mast cells also secrete IL-4, IL-5, IL-6, IL-8, and TNF- $\alpha$ , which increase airway smooth muscle (ASM) hyper-responsiveness, induce IgE synthesis, and recruit other immune cells, including T cells and eosinophils. In fact, mast cells are the only cell type that secrete preformed TNF (66) and can deliver it to the lymph nodes, further stimulating the immune response (81), especially by stimulating T cells through TNF (82,83). When TNF is administered by inhalation to humans, it induces both bronchial hyperresponsiveness (BHR) and sputum neutrophilia in normal subjects. TNF also exacerbates BHR in patients with asthma (84).

Moreover, mast cells counteract Treg cell suppression and promote the development of T17 cells involved in autoimmune diseases (85). In fact, mast cells can synthesize IL-17 (86). Mast cell-derived transforming growth factor-beta1 (TGF- $\beta$ 1) also induced the development of T17 cells (87). Mast cells can also induce TGF $\beta$ 1 expression in SMC via release of tryptase, resulting in differentiation of SMC into a more contractile phenotype (88).

Lung mast cell participation in asthma may not involve exocytosis of granular content typical of allergic or anaphylactic reactions. As a result, histologic studies are not likely to show evidence of mast cell activation. For instance, the ultrastructural appearance of activated mast cells often indicates a process of piecemeal degranulation and was associated with selective release of mast cell mediators (89). In particular, IL-1 induced release of IL-6 (90). CRH stimulated selective release of VEGF, which is also pro-inflammatory and vasodilatory (91). LPS induced release of TNF (92) without degranulation. Viral double-stranded RNA stimulated toll-like receptor-3 (TLR-3) to induce selective release of IL-13 (63). Moreover, TLR-4 regulated allergic airway inflammation through mast cell activation (93). TLRs are increasingly invoked in the development of airway inflammation (94), through regulation of mast cell function (94).

Proteases derived from isolated human lung mast cells stimulated by IgE/anti-IgE increased chemokine C-C motif ligand 8 (CCL8) and fibronectin production from cultured airway SMC (95). Moreover, alveolar mast cells had higher Fc $\epsilon$ RI expression in patients with mild allergic asthma than in patients with allergic rhinitis, implying that mast cells in asthma may present with a unique phenotype, thus making them even more relevant as targets for novel treatments (96).

## Stress, mast cells, and asthma

There is considerable evidence that stress worsens allergic diseases in general (97–99), as well as asthma (100,101). The effect of stress may be mediated through activation of mast cells (97). Mast cells infiltrated bronchial smooth muscle (BSM) in asthmatics and human lung mast cells adhered to BSM cells through type I collagen CD51 and CD44 (102).

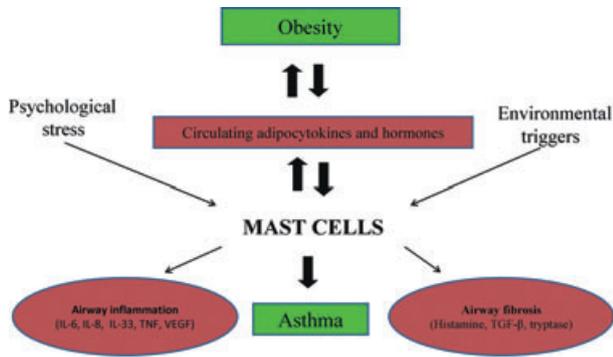
Stress typically results in secretion of CRH from the hypothalamus and activates the hypothalamic–pituitary–adrenal (HPA) axis. However, CRH is also released outside the CNS where it has pro-inflammatory effects, through mast cell activation (103,104). Moreover, human mast cells express mRNA and functional CRHR-1 (91), activation of which induces selective release of VEGF (91). Stress induces local release of CRH in the skin and stimulates skin mast cells leading to increased skin vascular permeability (73). Mast cells can also release large amounts of CRH (105).

CRH secreted from mast cells can decrease the ability of Treg cells to produce the immunosuppressant IL-10, thus further increasing inflammation (106). It is of interest that human adipose tissue expresses CRHR-1 and CRHR-2, as well as the CRH-related peptides urocortin and stresscopin (107), implying that CRH could affect adipose tissue both directly and indirectly, through mast cells. A recent study reported that prenatal stress was associated with increased cord blood IgE, and this correlation was stronger between a mother with a history of atopy and an offspring sensitive to dust mites (108).

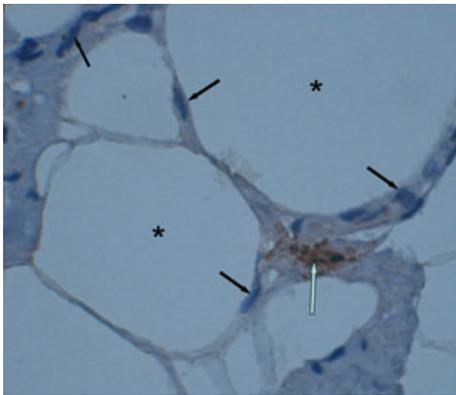
## Mast cells and obesity

We propose that mast cells are involved in both asthma and obesity by being the target and source of adipocytokines, ‘alarmins’ such as IL-9 and IL-33, and stress molecules including CRH and NT, secreted in response to the metabolic burden. Such molecules may act through mast cells, especially because they, as well as CRH and IL-33, are also expressed in human mast cells leading to autocrine effects (Fig. 1).

Mast cells are often found within WAT tissue (Fig. 2). In fact, WAT from obese humans and mice contain more mast cells than WAT from their lean counterparts (22). These mast cells also contribute to diet-induced obesity by producing inflammatory mediators such as IL-6, interferon-gamma (IFN- $\gamma$ ), TNF- $\alpha$ , IL-1 $\beta$  and CCL2 (22). Kit<sup>W-sh/W-sh</sup> mast cell-deficient mice fed a high-fat and carbohydrate-rich Western diet for 12 weeks gained significantly less body weight than wild-type (WT) congenic controls and had reduced serum and WAT levels of inflammatory cytokines, chemokines and proteases (22). Kit<sup>W-sh/W-sh</sup> mast cell-deficient mice or those mice receiving the rodent mast cell stabilizer, disodium cromoglycate (cromolyn), also had significantly lower concentrations of serum leptin than WT controls (22). Administration of leptin during allergen challenge of sensitized mice augmented allergen-induced airway hyperresponsiveness (AHR), even though it did not affect eosinophil influx or Th2 cytokine expression (31).



**Figure 1** Diagrammatic representation of the proposed interactions among adipocyte-derived molecules, mast cells, and their pro-inflammatory mediators in the pathogenesis of asthma and obesity.



**Figure 2** Light photomicrograph of human abdominal fat (obtained during plastic surgery of a 37-year-old Caucasian woman) showing adipocytes (asterisk), lymphocytes (dark arrow), and a tryptase-positive mast cell (open arrow).

### Clinical relevance and proposed treatment approaches

Current asthma treatment modalities are not as effective in the obese patient with asthma (15,16,109,110). This may be due to the fact that asthma associated with obesity may be of late onset, may involve noneosinophilic inflammatory cells, or other mast cell-dependent processes.

Inhibition of mast cell activation and/or secretion would certainly be desirable on many levels, as mast cells appear to be involved both in obesity and asthma, as well as serve as a link between these two diseases (Table 1). Unfortunately, there is no effective mast cell inhibitor clinically available. Cromolyn or the histamine-1 receptor antagonist ketotifen (administered intraperitoneally) reduced body weight and glucose intolerance in mice (22), but are ineffective in asthma. Moreover, cromolyn inhibits histamine secretion from rodent mast cells, but is a weak inhibitor of human mast cells (111,112).

Inhaled corticosteroids are heavily used for asthma, but mostly in order to reduce inflammation rather than inhibit

**Table 1** Summary of clinical relevance

There is an association between obesity and asthma
Mast cells are involved both in asthma and obesity and may regulate both
Psychological stress can worsen both asthma and obesity through mast cell activation
Inhibition of mast cells may be an effective treatment for both asthma and obesity
There is need for novel, effective, mast cell inhibitors
Unique quercetin/luteolin combinations with increased oral absorption may prove useful because of their anti-inflammatory, mast cell inhibitory, and insulin sensitivity improving actions

mast cell activation. A recent article reported that inhaled corticosteroids reduced the number of bronchial epithelial and smooth muscle mast cells, but not subepithelial mast cells (113). The anti-IgE humanized antibody omalizumab is also frequently used for severe asthma, but is characterized by 33% nonresponders (114). Reduction of the IgE appears to reduce bronchial inflammation and airway remodeling (115). Nevertheless, both corticosteroids and omalizumab have the potential of serious side effects, including infections. A new approach involved aggregation of the FcεRI with the low-affinity IgG receptor (FcγRIIb) by a novel bispheric fusion protein that led to more effective allergic basophil inhibition of cytokine release *in vitro* than omalizumab (116).

Certain natural flavonoids (117), such as quercetin and luteolin, possess potent antioxidant, anti-inflammatory and mast cell-blocking actions (118,119), making them potential candidates for prophylactic treatment of asthma and the metabolic syndrome. In fact, aerosolized quercetin was used in experimental murine allergic asthma (120). Moreover, quercetin mimics the action of glucagon-like peptide-1, a promising treatment candidate for type 2 diabetes (121). Luteolin, the flavone of the flavonoid quercetin, can inhibit human mast cells and mast cell-dependent T-cell activation (83), as well as adipocyte-dependent activation of macrophages (122). Luteolin also improves insulin sensitivity of the endothelium (123).

Unfortunately, flavonoids are poorly absorbed orally in powder form (<10%) and are rapidly metabolized (117). Better formulations using liposomal or phosphatidyl choline-carrier luteolin could provide increased delivery and oral absorption.

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### Conflict of interest

There is no conflict of interest. Dr. Theoharides is the recipient of US Patents No. 6,624,148; 7,115,278; and 7,759,307,

covering the use of flavonoids in the treatment of CAD, which were assigned to Theta Biomedical Consulting and Development Co. Inc. (Brookline, MA).

### Author contributions

Dr. Theoharides wrote the manuscript, and the rest of the authors contributed to it by providing bibliographic informa-

tion, graphics, and corrections. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

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