

Obesity alters inflammatory response in the pathology of asthma (Review)

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Abstract. Obesity is one of the comorbidities in patients with asthma and obese patients with asthma present with a distinct phenotype with more severe disease outcomes and reduced responsiveness to standard therapies. Although the full mechanisms of obesity-related asthma are still not completely understood, abnormal immune responses have been demonstrated to have a critical role in asthma pathogenesis. The present review summarizes the data from clinical, epidemiological and animal studies to provide an updated understanding of the immune responses in obesity-related asthma, as well as the effect of various factors, such as oxidative stress, mitochondrial dysfunction, genetics and epigenetics, on asthmatic inflammation. Further studies on the in-depth mechanisms are still required to develop novel preventive and therapeutic strategies for patients with asthma combined with obesity.

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1. Introduction

As a prevalent chronic inflammatory disease of the airways, asthma is distinguished by a highly diverse etiology and a variety of clinical features, including airway hyperresponsiveness (AHR), underlying inflammation, fluctuating and recurring symptoms and airflow restriction (1). According to the difference in the type of airway inflammation caused by the immune response, asthma may be divided into type 2 inflammation and non-type 2 inflammation. Type 2 inflammatory asthma is mostly driven by allergens, including house dust mites (HDMs), pollens or animal dander, and involves T helper type 2 (Th2) and innate lymphoid cell (ILC) 2 immune cells, causing the upregulation of type 2 cytokines, such as IL-4, IL-5 and IL-13, and leading to airway inflammation and asthma attack. However, non-type 2 asthma may be triggered by air pollutants, viral or bacterial infection, obesity, smoking or other irritants. Immune cells including neutrophils, Th1 cells, ILC1s, natural killer (NK) cells and macrophages participate in non-type 2 asthma, which causes the upregulation of non-type 2 cytokines and induces the occurrence of the disease (2). Typical asthma symptoms, including coughing, wheezing and shortness of breath, may be frequently observed in type 2 inflammatory asthma (3). In addition, comorbidities such as allergic rhinitis, atopic dermatitis, food allergies or non-allergic disorders, such as obesity and gastroesophageal reflux, may coexist with asthma (4). As the proportion of obese individuals continues to increase, obesity-related asthma has

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become more frequently identified, becoming a particular challenge for asthma management due to increased medication use, decreased steroid responsiveness, longer hospitalization, poorer quality of life and greater severity of the disease compared with ordinary asthma patients (5).

According to studies of asthma phenotypes and endotypes, asthma associated with obesity has recently been confirmed as one of the major non-type 2 driven phenotypes and a unique respiratory metabolic phenotype (6,7), characterized by increased levels of metabolites (8). Obesity tends to involve lymphocyte responses of Th1 and T helper 17 (Th17) cells rather than the classic Th2 cell response observed in asthma (9). Rastogi *et al* (10) reported that compared with those in children with asthma alone, CD4+ Th1 cell levels in the peripheral blood of obese asthmatic children were increased, and the Th2 cell response was not enhanced (11), implying a change in the function of lymphocytes in obese patients, and that metabolic function may be involved in the effect of lymphocytes (12). Furthermore, high levels of neutrophils and fewer eosinophils were also identified in the sputum of obese asthmatic patients (13). In the aforementioned studies, cell function was found to be decreased, which is consistent with the fact that most patients with obesity-related asthma have Th1 and Th17-enhanced asthma but not Th2-enhanced asthma. However, the type of inflammation in obesity-related asthma is still controversial. The inflammation covered in Chapter 2 onwards mostly refers to the more common type 2-driven inflammation, rather than non-type 2-driven inflammation, which is a special asthma phenotype. Studies involving non-type 2 inflammation will be highlighted in the sentences of this article.

Obesity is primarily brought on by complex metabolic dysregulation that is caused by an imbalance between calorie intake and expenditure (14). Obese individuals exhibit a specific non-type 2-driven chronic subclinical inflammation, which may lead to asthma exacerbation, aggravate airway inflammation and impair lung function (15). However, more research is required to fully comprehend the interactions between the adipose tissue and the lung, as well as the role served by innate and adaptive immune cells, and the molecular basis of these intricate immuno-metabolic interventions (Fig. 1).

The present review provides an update on the association between obesity and asthma, paying particular attention to current trials, studies and understanding of the probable metabolic-inflammatory route, to provide ideas for future studies and potential treatments.

2. Obesity and asthma

Association between obesity and asthma. Obesity [body mass index (BMI) ≥ 30 kg/m²] and overweight status (BMI ≥ 25 kg/m²) are linked to a higher probability of developing chronic noncommunicable diseases, a lower quality of life, exacerbation of daily symptoms and an increased need for rescue medications (5,16). In a multicenter retrospective cohort study of emergency department (ED) patients aged 18 to 54 years with asthma exacerbation from 48 EDs across 23 US states during 2011 and 2012, obese adults presenting to the ED with asthma exacerbation were determined to have a higher risk of hospitalization compared with normal-weight adults (17).

In addition, a k-means cluster analysis in three independent asthma populations has validated the heterogeneity in clinical characteristics and inflammatory biomarkers of asthma in obese individuals (18). Therefore, it is assumed that obesity may cause persistent systemic inflammation due to inflammatory mediators of the adipose tissue, thus elevating the risk of airway obstruction and AHR in patients with asthma, leading to asthma exacerbations (16). Furthermore, the BMI, waist circumference or waist-to-height ratio of obese populations are positively associated with current asthma, although other metabolic syndrome components are not found to be strongly related to current asthma (19-22). However, asthma readmissions have also not been observed to be markedly related to obesity or overweight status (23).

Since obesity is a major risk factor for poorly controlled asthma, the factors contributing to the pathogenesis of obesity-related asthma have attracted increasing attention. To a certain extent, dietary compositions have been reported to lead to an abnormal metabolic process, which causes obesity, as well as airway responsiveness and inflammation in patients with asthma (14). Obesity-causing diets are often high in red and processed meats, fats, sugar and fried meals, while being low in fiber. Such a dietary pattern is associated with the immune system and asthma pathogenesis through changed epigenetics factors, enhanced oxidative stress, abnormal expression of adipokines and disturbed intestinal flora, causing chronic inflammatory state, impaired lung function and respiratory symptoms (24). An animal study revealed that dietary fiber may influence the immune response through short chain fatty acids (SCFAs) as early as during *in utero* development (25). In addition, a high-fat diet (HFD) may lead to airway disease even if it does not result in obesity, as illustrated by studies in both mouse models and humans (26,27).

Epidemiology of obesity-related asthma. According to official documentation from the American Thoracic Society published in 2010, obesity is a risk factor for adult asthma and the concept is widely accepted due to its in-depth study (28). Depending on the age of onset, obesity has been demonstrated to be associated with different asthma phenotypes and endotypes (29). Inadequate lung function, obesity and metabolic syndrome were found to be associated in a US study of teenagers (30). Obese patients with early-onset asthma have a greater AHR, more severe airway obstruction and an increased exacerbation risk compared with obese patients with late-onset asthma, with similar levels of IgE and eosinophilic inflammation (29). According to a study from Brazil, severe asthma in adolescents was markedly associated with certain aspects of metabolic syndrome, particularly insulin resistance, but not with the BMI (31). This suggests that the BMI may not be a reliable parameter for severely obese children and adolescents due to being an artificially defined indicator (32). While it has been demonstrated in a number of studies that obese children have an increased risk of developing asthma, a different study reported the opposite, finding that a history of asthma and medication had an impact on childhood and adolescent obesity (33). These specific features in asthmatic children imply that the phenotype of children should be distinguished from late-onset obesity-related asthma in adults. The aforementioned results suggest that obesity is more likely to

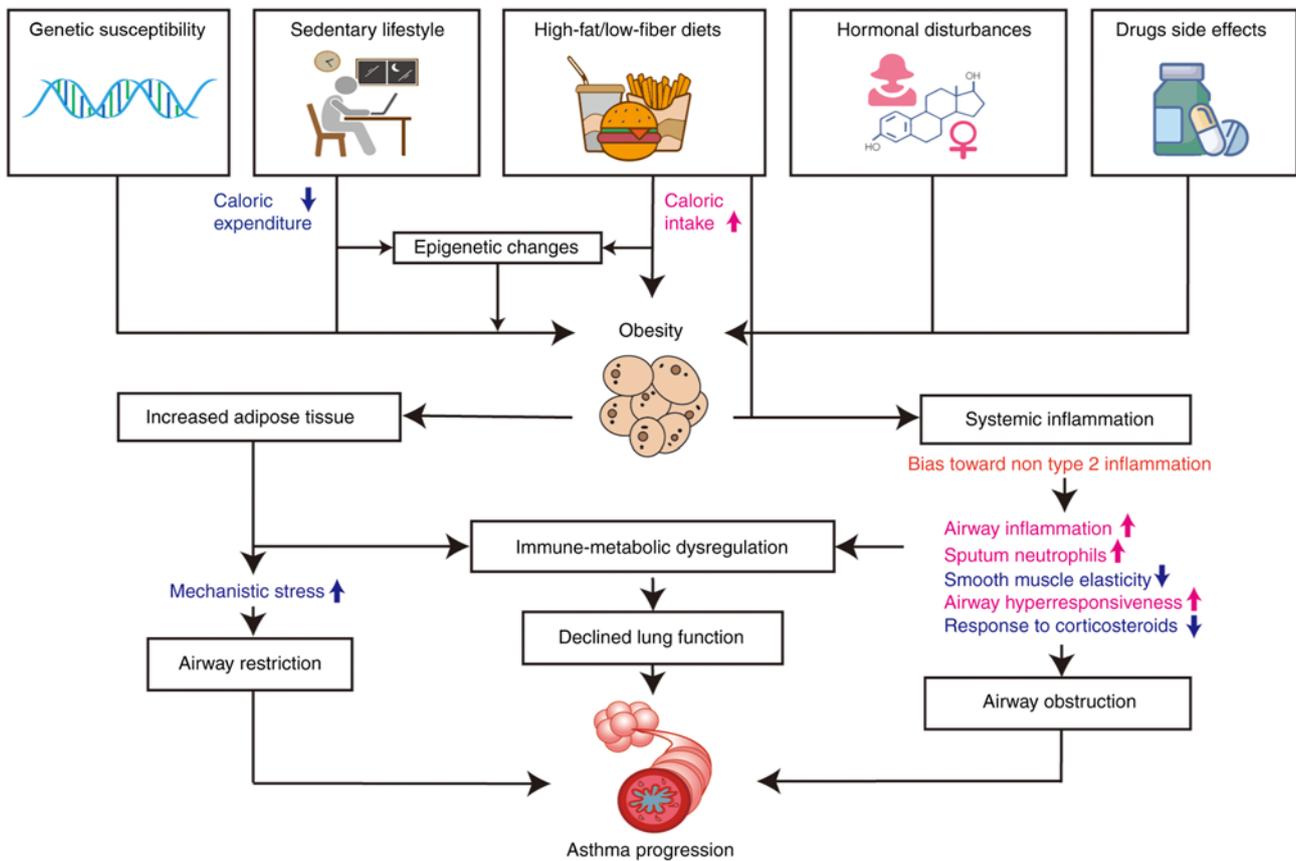


Figure 1. Pathogenesis of obesity-related asthma. Obesity may be caused by a number of factors and is accompanied by increased adipose tissue and the appearance of chronic systemic inflammation. The increased adipose tissue increases the mechanical burden of bronchial physiological activities and cause airway restriction. Systemic inflammation with a bias towards non-type 2 causes airway inflammation, airway hyperresponsiveness and low sensitivity to glucocorticoids, causing airway obstruction. These symptoms can lead to decreased lung function and demonstrate the immune-metabolic dysregulation present in obesity-related asthma. Airflow restriction and airway obstruction contribute to the progression of asthma.

be an asthma comorbidity for early-onset asthma, which is less severe but less responsive to treatment, whereas obesity has a causative influence on late-onset asthma, which is generally severe. Furthermore, it cannot be ruled out that a sizeable portion of adult patients with obesity-related asthma were children who originally had type 2-driven asthma, with obesity developing later due to other factors (34). Therefore, further research is still needed to determine the underlying causes of obesity and asthma in various age groups.

The notable characteristics of the non-type 2-driven phenotype of obesity-related asthma are more frequently observed in women, and female sex is considered to be a key component of this asthma phenotype (35). Obesity may increase the chance of developing asthma in women, but not in men, according to a Canadian study (36). In addition, it has been revealed that the BMI is substantially associated with asthma severity only in women and not in men, suggesting that hormonal state, particularly during the early menarche, may serve a role in asthma pathogenesis (37). Overweight and obesity among girls before pubertal onset can advance the age of onset of puberty and the age of menarche, providing evidence for the association between obesity and hormonal state (38). Only among women, central adiposity has been reported to exhibit a strong association with asthma (39). In obese women but not in obese men, obesity has also been revealed to be associated with moderate AHR (40). In brief, the relationship between

obesity and asthma is particularly notable in women and the development of asthma may be influenced by hormone levels and the activity of estrogens (37). However, no consensus has been reached on whether female sex should be recognized as a risk factor in obesity-related asthma (22). Although sex has been described as having no influence on obesity-related asthma in children (39), according to a meta-analysis, maternal obesity during pregnancy may increase the risk of asthma in children; however, since the inclusion criteria were not carefully adhered to, the findings of the study may require more substantiating evidence (41).

As a result, there are currently numerous unrecognized epidemiological patterns of obesity-related asthma, particularly in children and adolescents. It is still unclear what distinguishes the various endotypes of asthma in obese individuals and this needs to be further clarified (Fig. 1).

3. Possible pathogenesis of asthma in obese individuals

Numerous epidemiological studies have demonstrated the link between obesity and asthma; however, the underlying mechanisms are still unclear and further investigation through various clinical and animal experiments is ongoing. Metabolic disorders impair airway function in obese individuals through various mechanisms such as HFD, disordered L-arginine/nitric oxide pathways, mitochondrial dysfunction, insulin resistance

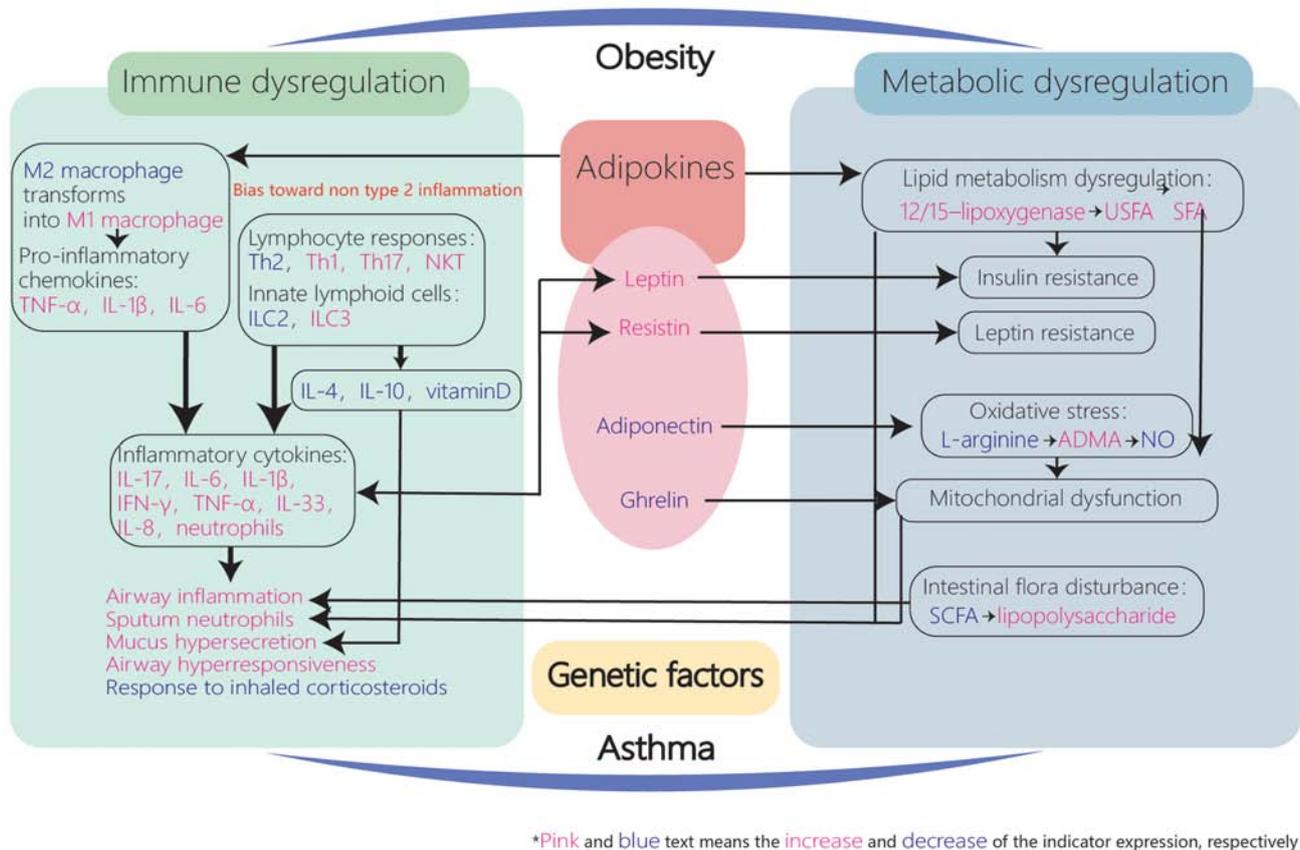


Figure 2. Immuno-inflammatory mechanisms of obesity-related asthma. Adipokines including leptin, resistin, adiponectin and ghrelin may contribute to metabolic and immune dysregulation in patients with asthma via complex interactions and lead to inflammation which bias toward non-type 2, implying the important role of increased adipose tissue in asthma progression. TNF- α , tumor necrosis factor- α ; Th, T helper type; IL, innate lymphoid; ILC, innate lymphoid cell; NKT, natural killer T; IFN, interferon; USFA, unsaturated fatty acids; SFA, saturated fatty acids; ADMA, asymmetric dimethylarginine; NO, nitric oxide; SCFA, short chain fatty acid.

and abnormal lipid metabolism. Macrophages, lymphocytes, intestinal floras and certain adipokines produced by adipocytes in adipose tissue are important in regulating metabolic balance, with a strong connection to the immunological response in patients with obesity-related asthma (42). Oxidative stress, mitochondrial dysfunction, genetics and epigenetics factors, which are involved in the abnormal immune responses in asthma, may also be associated with metabolic dysfunction, indicating their crucial roles in the pathogenic mechanisms of obesity-related asthma (43) (Fig. 2).

Inflammation in obesity-related asthma

Cells. Macrophages, neutrophils, ILCs, NKT cells, Th1 cells and Th17 cells secrete a variety of cytokines and chemokines under stimulation, acting on bronchial smooth muscle, eventually leading to a series of asthma symptoms such as tracheal constriction, airway remodeling, increased mucus secretion, AHR and impaired lung function (44). However, obese patients with asthma have immune responses that differ from those of normal-weight patients with asthma. Besides studies focusing on innate immunity in inflammation of patients with obesity-related asthma, studies focusing on the adaptive immune system have also attracted attention, helping to explore the potential mechanisms of the specific immune responses of obese patients with asthma (9) (Table I).

i) Macrophages. Normal lung tissues have M1 and M2 types of macrophages to maintain the balance of pulmonary function and status (45). Immune cells in normal adipose tissue typically comprise M2 macrophages, CD4+T cells and regulatory T cells, which may collectively adjust heat production, the immune response and fat metabolism. Long-term overnutrition may lead to hypertrophy, vascularization, hypoxia and necrosis of adipose tissue, leading to macrophage infiltration in adipose tissue and surrounding necrotic tissue, increasing the levels of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor- α (TNF- α). Along with the over-expressed pro-inflammatory cells (M1 macrophages), integrins (CD11b and CD11c) and other metabolic endotoxins and adipokines, anti-inflammatory M2 macrophages transform into pro-inflammatory M1 macrophages (46). When inflammatory factors released by adipose tissue reach the lungs through the circulatory system, airway inflammation and AHR may occur (47,48). The abnormal activity and metabolism of macrophages may be an important mechanism in the pathological process of obesity-related asthma.

As cells with high inflammatory activity, M1 macrophages may secrete various pro-inflammatory adipokines and chemokines, which lead to a state of subclinical inflammation in adipose tissues (49), and these adipokines and chemokines include TNF- α , IL-1 β , IL-6 and monocyte chemoattractant protein-1 (50), the elevated expression of which is observed

Table I. Cells and adipokines involved in obesity-related asthma pathogenesis.

A, Cells			
Name	Effect	Expression in obesity-related asthma and possible mechanism	(Refs.)
M1 type of macrophages	Pro-inflammatory	Increased Increased secretion of TNF- α , IL-1 β , IL-6 and MCP-1	(50)
M2 type of macrophages	Anti-inflammatory	Decreased Decreased secretion of TGF- β and prostaglandin E2	(53)
Th17 cells	Pro-inflammatory	Increased IL-17 generated by Th17 cells secretes increased IL-6, TNF- α and IL-8	(58)
Th1 cells	Pro-inflammatory	Increased Increased secretion of IL-2, IL-3 and TNF- α	(13)
Th2 cells	Pro-inflammatory	Elusive	
Eosinophils	Pro-inflammatory	Elusive	
Neutrophils	Pro-inflammatory	Increased	(70)
NKT cells	Pro-inflammatory	Increased	(65)
B, Adipokines			
Name	Effect	Expression in obesity-related asthma and possible mechanism	(Refs.)
Leptin	Regulation of energy balance and appetite Pro-inflammatory effect	Increased Increased secretion of IL-6, TNF- α and interferon- γ , activation of mast cells and NF- κ B, and imbalance of the regulation of Th1/Th2 cells	(81)
Resistin	Reduces the sensitivity of the body to insulin Pro-inflammatory effect	Increased Boosts the activation of NF- κ B and secretion of TNF- α , IL-6 and IL-1	(80)
Adiponectin	Regulates various metabolic processes and energy balance Anti-inflammatory effect	Decreased Weakens effects that inhibit IL-6 and TNF- α	(74)
Ghrelin	Regulates energy balance and appetite Anti-inflammatory effect	Decreased Weakens effects that inhibit IL-1, IL-6 and TNF- α	(92)

MCP-1, monocyte chemoattractant protein 1; Th1, type 1 T-helper; NKT, natural killer T.

in obesity-related asthma even without antigen activation (51), implying a role of M1 macrophages in asthma pathogenesis. TNF- α secreted by M1 macrophages may bind to receptors on airway smooth muscle, contract the muscle and induce intracellular signal transduction and inflammation (11), which are positively related to the BMI of patients with asthma (52). Obese mice lacking TNF- α receptor 2 were not observed to have enhanced airway reactivity, indicating the importance of TNF- α activation in asthma pathogenesis (51).

M2 macrophages inhibit inflammation through secretion of efferocytosis-related molecules and anti-inflammatory mediators such as transforming growth factor- β and prostaglandin E2 (53). In a previous study, efferocytosis and biomarkers reflecting the function of M2 macrophages were decreased in the sputum of obese asthmatic patients, while the levels of M1 macrophages were higher than those of patients with asthma with a normal body weight (54), implying that the effect of suppressing inflammation was

weakened because of the excessive polarization of M2 macrophages (55).

ii) Lymphocytes. Obesity tends to represent the lymphocyte response of Th1 and Th17 cells, associated with the increased portion of Th1 and Th17 cells, which is associated with the altered portion of Th2 and regulatory T cells (43).

IL-17 can directly induce airway hyperreactivity (56). Increased IL-17 (secreted by ILC3s) and increased activity of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome in lung tissues of HFD-induced mice (57) suggested that IL-17 may promote inflammation in obese individuals. Furthermore, IL-17 generated by Th17 cells may stimulate the production of inflammatory molecules such as IL-6, TNF- α and IL-8 by activating the mitogen-activated protein kinase (MAPK) or nuclear factor- κ B (NF- κ B) signaling pathway, thus promoting airway inflammation (58). In addition, airway neutrophilic leukocytosis is a feature of obesity-related asthma, while lung neutrophilic aggregation is closely associated with the excessive secretion of IL-17, IL-6 and TNF- α from Th17 cells, which may aggravate inflammatory manifestations in airways (59,60).

Compared to individuals with a normal BMI, increased Th1 cell levels in adipose tissue of obese individuals cause the immune system to enter a pro-inflammatory state. Furthermore, cytokines IL-2, IL-3, TNF- α and interferon- γ produced by adipocytes and immune cells to maintain tissue integrity may further promote inflammation of the airways (13). Reduced regulatory T cells in adipose tissue may also be associated with obesity, causing inflammation and insulin resistance (61).

ILC2s and ILC3s, produced by common helper innate lymphoid progenitors, may be associated with the exacerbation of allergic airway inflammation in activating gene 12/2 and leptin-deficient HFD-HDM mice, indicating the involvement of ILCs (34,57). Furthermore, NLRP3 may act as a key regulator of the innate immune response of the host (62). NLRP3 and IL-17 (secreted by ILC3) have also been found to be important mediators for the acceleration of AHR in mouse models. After knockout of the genes related to adaptive immunity in HFD-fed mice, AHR remained measurable, demonstrating the independent role of innate immunity in the mechanism (57).

The effect of Th2 cells on obesity-related asthma remains disputed. IL-33, produced by epithelial cells, helps maintain the integrity and metabolism of adipose tissue. IL-33 induces ILCs to produce IL-5 and IL-13, which accelerate the activation of eosinophils. Eosinophils emit IL-4, which contribute to polarizing M2 macrophages and diverging beige adipocytes (63,64). Therefore, anti-IL-33 biologics may be a potential therapeutic in certain cases. The association between obesity and Th2 type CD4+ cell differentiation remains controversial. Certain studies have reported AHR and increased secretion of Th2 cytokine and eosinophilia in HFD-induced obesity (34,65). Furthermore, in *in vitro* research, Th2 cells differentiated from human CD4+ cells were associated with melanin hormone production, which was associated with increased appetite and obesity (66), revealing a comparable pathogenic pathway for the Th2 response and obesity.

The important role of lymphocytes in asthma has been demonstrated, while the varied phenotypes and endotypes

of asthma related to distinct immune responses, particularly for obese patients with asthma, remain unclear. There is still more research to be done on the various lymphocyte subtypes involved in immunological processes.

iii) Eosinophils. Although advances have been achieved in type 2-driven asthma, non-type 2-driven asthma is poorly understood. Studies have found that obese female patients often present with typical non-type 2-driven asthma, which is clearly associated with metabolic imbalance (35).

As an important biomarker of type 2-driven and allergic asthma, the role of eosinophils in obesity-related asthma remains contentious. In animal studies, different mouse models that imitate human obesity-related asthma have varying eosinophil levels. HFD-ovalbumin (OVA)-induced mice exhibited reduced eosinophils, increased IL-10 and upregulated inflammatory cytokines IL-5 and TNF- α in their bronchoalveolar lavage fluid (BALF), while the eosinophil levels gradually increased while being transported from bone marrow to lung tissues (67). In addition, increased levels of eosinophils and AHR have also been reported in BALF of an HFD-HDM-induced mouse model (34). Furthermore, in another study, HFD-OVA-induced obese mice exhibited lower susceptibility to allergic sensitization, which was positively associated with increased airway eosinophilia, anti-OVA IgE antibodies and IL-6 (68). Considering that AKR mice are more likely to reflect the obesity and AHR phenotypes, the various usages of sensitizing and stimulating substances and the diverse sampling and detection modes in mouse models, the aforementioned results may need further verification. On the other hand, in a clinical investigation (69), asthma was reported to be positively associated with obesity with or without increased eosinophil inflammation in overweight asthma patients. In addition, eosinophils and IgE levels were identical in obese and non-obese asthmatic children.

Despite the fact that obesity-related asthma is regarded as the primary subtype of non-type 2-driven asthma, no direct evidence of reduced eosinophils has been found in animal and clinical studies. The clinical co-existence of asthma and obesity may not only be due to non-type 2-driven immunity due to differences in individual behavior, suggesting that further studies on the critical factors that may trigger the complex interactions are required.

iv) Neutrophils. Previous studies suggest that neutrophils may serve a role in the etiology of obesity-related asthma. A previous study revealed higher neutrophil levels in the blood and sputum of obese asthmatic patients, particularly in women (70). However, neutrophils were considerably reduced in obese female asthmatic patients after losing weight and in male patients after reducing saturated fatty acid (SFA) intake (71). Even in asthmatic patients without obesity, an HFD was able to markedly increase neutrophils and impair the effect of bronchodilators (27).

This evidence suggests that neutrophils may be involved in the pathogenesis of obesity-related asthma, particularly in women, as a direct result of obesity or an HFD.

v) Others. NKT cell levels were found to be decreased in common obesity with a slightly increased degree of activation, while the expression and activation of NKT cells were more noticeably increased in obese patients with asthma (65), suggesting that NKT cell differentiation is inhibited in obesity

and more active in obesity-related asthma, implying a positive association with airway inflammation.

Various cellular molecules have been observed to be related to immunologic pathways, and thus, potentially affect the progression of airway inflammation. CD38, as an important metabolic enzyme located on the surface of plasma cells, T cells, NK cells, dendritic cells and other cells, serves a role in T-cell priming, as well as dendritic and neutrophil cell migration (72). Highly expressed CD38 in lungs of HFD-OVA obese mice was found to induce AHR, potentially by mediating the upregulation of TNF- α (73).

In conclusion, abundant studies in humans and animals have provided evidence for how immune responses impact the pathogenesis of asthma in obese individuals. However, it is still unclear how immunity and metabolism interact in detail. Obesity-related asthma has been observed to be closely associated with innate immune responses, while the potential role of adaptive immune responses still requires further research.

Adipokines. In obesity, adipose tissue usually exhibits the states of hypertrophy and hyperplasia, giving rise to increased levels of pro-inflammatory mediators and higher secretion of inflammatory cytokines, including TNF- α , IFN- γ , IL-6 and IL-17, leading to dysregulated fat metabolism and airway inflammation (28). Furthermore, adipokines are peptide substances produced by adipose tissue, which may act as critical mediators in both metabolism and the immunological response through their endocrine activity that reveal the functional state of adipose tissue (74) (Fig. 2 and Table I).

i) Leptin. The adipokine leptin, an important mediator secreted by adipose tissue, binds to and activates the leptin receptor (LEP-R) in the brain and activates JAK-STAT3, suppressing neuropeptide Y and agouti-related protein, which increase food intake, and increasing proopiomelanocortin and corticotrophin-releasing hormone, which decrease food intake, and thus, regulates the energy balance and appetite through a negative feedback mechanism between adipose tissue and the hypothalamus (75). When fat cells increase, leptin levels also increase and leptin binds to LEP-R to send signals to increase satiety, thus controlling food intake, as well as to promote energy expenditure (76). Congenital leptin deficiency, high but ineffective leptin and leptin resistance may lead to obesity (77).

Clinical research indicated that leptin was upregulated in obese individuals, which was positively associated with AHR, and may be normalized after weight loss surgery (48). In another clinical study, patients with obesity-related asthma demonstrated elevated levels of leptin, which may trigger asthmatic inflammation in the obese phenotype of asthma (78). Furthermore, leptin resistance may be developed in obese individuals, which may further exacerbate obesity by causing a greater sense of hunger (79), which is an adverse factor in asthmatic complications. However, in a clinical study, leptin levels were not found to be associated with asthma (80), indicating the possibility that leptin is involved in asthma as a regulator rather than an etiologic factor in asthma development. Obese mouse models with elevated leptin levels also exhibit an exacerbation of allergic asthma and increased AHR (79,81). Studies found that, besides regulating appetite, leptin may also induce the pro-inflammatory state by increasing IL-6, TNF- α and interferon- γ , activating mast cells and NF- κ B, and unbalancing

the regulation of Th1/Th2 cells (81). Furthermore, the pathway for leptin to affect allergic responses was investigated in mice, indicating that rapamycin complex 1, MAPK and STAT3 in Th2 cells may be involved in enhancing the production of Th2 cytokines to produce more IL-4, IL-13 and IL-5, which cause airway symptoms (82).

Although leptin is assumed to be a pro-inflammatory factor, there is no precise *in vitro* or *in vivo* evidence to support this hypothesis. Interrelations of leptin with allergic reactions still need further proof and investigation.

ii) Resistin. Resistin is another hormone released by adipose tissue that may reduce the sensitivity of the body to insulin, leading to insulin resistance (83). Resistin has been observed to be elevated in obesity, which may boost the activation of NF- κ B and secretion of inflammatory cytokines, such as TNF- α , IL-6 and IL-1, which may in turn stimulate resistin production, contributing to severe exacerbations of asthma in obese patients (78). Furthermore, overweight patients with asthma have higher resistin and leptin levels than normal-weight patients with asthma (78), and high resistin levels have been demonstrated to be negatively associated with lung function (84), suggesting a potential role for resistin in asthmatic processes. However, a study reported no difference in resistin levels between obese and non-obese patients with asthma, indicating that resistin may be a predictor of asthma risk and resistin/adiponectin may act as a forced expiratory volume in 1 sec predictor in asthma (85). At present, the role of resistin in obesity-related asthma is still controversial and requires further exploration.

iii) Adiponectin. Adiponectin is a peptide hormone and the most abundant adipokine in adipose tissue, and is involved in the regulation of various metabolic processes and energy balance (86), affecting anti-inflammation pathways and cellular metabolism (87).

In contrast to leptin, resistin and TNF- α , adiponectin levels may decrease with obesity, with higher neutrophil and eosinophil levels, and pulmonary vascular remodeling, demonstrating a diminished anti-inflammatory impact linked to asthma attacks (87,88). Adiponectin can inhibit airway inflammatory and oxidative stress (87), potentially by inhibiting IL-6 and TNF- α , which are important pro-inflammation factors in asthma mechanisms (74). HFD-OVA mouse models have indicated its regulatory effect on cellular metabolism via adenosine monophosphate-activated protein kinase signaling pathways (87), demonstrating that adipokines may act not only on immunity but also metabolism, thus serving an important role in asthma associated with obesity. However, contradictory results have been obtained in clinical studies, which found no statistically significant difference in adiponectin levels between obese and non-obese adults with asthma (85). Furthermore, adiponectin levels may differ in female and male adults due to the inhibitory effect of testosterone on adiponectin (89), which requires further exploration.

iv) Ghrelin. Besides leptin, ghrelin is another appetite hormone regulating metabolism and energy balance (90), causing increased food intake and decreased fat utilization (91). The expression of pro-inflammatory cytokines such as IL-1, IL-6 and TNF has been demonstrated to be inhibited by ghrelin (92). Furthermore, obese individuals exhibit less ghrelin expression and an impaired inhibitory effect of ghrelin

on inflammation, which is considered to be a physiological protective mechanism to regulate the energy balance (93).

In brief, adipokines appear to be possible mediators that affect the immune responses in obese patients with asthma, although the detailed mechanisms still require to be determined.

Oxidative stress. The metabolic imbalance in obese patients with asthma may be closely associated with oxidative stress. Reduced levels of L-arginine with high levels of asymmetric dimethylarginine (ADMA) may promote the uncoupling of nitric oxide synthase (NOS) and inhibit the production of NO, resulting in decreased production of NO and excessive production of reactive oxygen species (ROS) (94), which may in turn impair the airway physiological function of NO bioavailability and bronchiectasis (95). ROS, performing as oxidants in the human body, are normally produced in small amounts by mitochondria (96), while altered metabolism in mitochondria caused by an obesity-related chronic inflammatory state may lead to the overexpression of ROS, which can in turn trigger mitochondrial dysfunction (97). Excessive ROS may disturb cellular homeostasis and lead to an over-oxidation state in cells, reported as a key element in oxidative stress, which has been linked to asthma etiology and an increase in airway inflammation (98) (Fig. 2).

Obesity may cause mitochondrial dysfunction by overwhelming the Krebs cycle and the mitochondrial respiratory chain, leading to increased ROS formation (99,100). HFD mouse models exhibited higher levels of oxidative stress indicators, including increased uncoupled inducible NOS and lower NO, but without enhanced airway inflammation (100,101). Elevated levels of ROS resulting from infiltrating immune cells and consequential oxidative stress are implicated in the pathological processes underlying asthma. When combined with obesity, oxidative stress is exacerbated, leading to tissue damage and promoting airway inflammation and hyper-responsiveness (102). However, there is no certain evidence that obesity-induced overexpressed ROS can potentiate type 2 or non-type 2 inflammation in asthma. The plasma L-arginine/ADMA ratio was found to be decreased in patients with late-onset asthma, with more evident airway symptoms, worse lung function and reduced fractional exhaled NO (103), which is negatively associated with the BMI (104,105). Obese patients with asthma may have higher oxidative stress biomarkers levels and NO deficiency, causing airway dysfunction, increased comorbidities and impaired glucocorticoid sensitivity (106,107).

In summary, oxidative stress manifesting with altered L-arginine and NO metabolism may act as a potential pathway in obese patients with asthma. Furthermore, key inflammatory cytokines in asthma, including IL-4, are markedly associated with obesity and mitochondrial dysfunction (105). IL-4, as an allergic inflammatory mediator, may induce ADMA aggregation in airway epithelial cells, leading to increased ROS and mitochondrial dysfunction, which are also associated with the immune responses in asthma (105), resulting in airway damage and remodeling (106).

Fatty acids. Previous research has indicated that disturbances in lipid metabolism may be linked to the mechanism of

obesity-induced asthma and may be one of the possible causes of the failure of traditional therapies.

During the metabolism of unsaturated fatty acids (USFA), 12/15-lipoxygenase, which acts as a catalyzer in the hydrogenation and oxidation of USFA, may be involved in insulin resistance in obese individuals (108). In addition, 12/15-lipoxygenase is involved in mitochondrial dysfunction. The disruption of calcium homeostasis and subsequent mitochondrial dysfunction in airway epithelial cells, caused by overload of mitochondrial calcium, may lead to the manifestation of asthma symptoms (109). IL-4, an important inflammatory agent, may also induce mitochondrial dysfunction (110), causing increased neutrophil aggregation and more severe airway damage (111) (Fig. 2).

On the other hand, SFA metabolism has also been reported to be associated with immunological responses. HFD-induced obesity may be associated with higher levels of SFA and nutritional factors, which may trigger immune-metabolic disorders (112), leading to AHR and neutrophilic airway inflammation (113-115). When palmitic acid, the primary SFA component in HFD, was added directly to a HDM mouse model, similar effects on the airways were also observed (116).

Intestinal flora. Intestinal floras act as major biological barriers and immunomodulatory function regulators to the human body. Obesity may cause intestinal flora disorders, leading to increased intestinal mucosal permeability and decreased SCFA, involving the immunomodulatory dysfunction in asthma (117).

Studies have revealed increased lipopolysaccharides in the plasma of obese asthmatic patients and HFD-induced lipopolysaccharides may enter the blood circulation through the intestinal mucosa with increased permeability, activate the NF- κ B signaling pathway and produce pro-inflammatory molecules such as TNF- α and IL-6, eventually resulting in AHR and asthma exacerbation (118). On the other hand, an HFD or low-soluble-fiber diet may alter the gut microbiome and is associated with lower levels of SCFAs that enter the circulation, thereby lowering the ability of SCFAs to inhibit dendritic cells to stimulate allergic inflammation, causing augmented allergic airway inflammation (117). Furthermore, a high-fiber diet may alter the composition of the intestinal and lung microbiota of mice. Intestinal microbiota metabolize fiber, increase circulating SCFA levels and further regulate the differentiation and activation of regulatory T cells, improving the immune environment of the lungs, thus inhibiting the occurrence of allergic inflammation and weight gain (117).

Although several studies have implied the role of intestinal floras in asthma mechanisms, studies in this field are still lacking and further exploration is required.

Genetics. As a more precise predictor of asthma features than family history, the high-risk genotype of asthma commonly overlaps with that of obesity (119), implying similarities in gene expression rooted in lipid metabolism and allergic mechanisms (120). Numerous susceptibility loci for asthma and obesity have been identified, including adrenoceptor β 2 gene (ADRB2), nuclear receptor subfamily 3 group C member 1 (NR3C1) and TNF- α gene (121,122) (Table II). ADRB2 affects the sympathetic nervous system, thus exerting an influence on the respiration and metabolism systems (123).

Table II. Genes and loci relevant to obesity-related asthma.

Introduction	Gene and loci	Mechanism of action	(Refs.)
Susceptibility loci for asthma and obesity	ADRB2	Affects the sympathetic nervous system, thus influencing respiration and metabolism	(118-120)
	NR3C1	The glucocorticoid receptors encoded by NR3C1 regulate airway inflammation	
HFD-upregulated gene	TNF- α gene	TNF- α induces immune-inflammatory responses.	(121)
	CHI3L1 gene	The expressed products are related to obesity and asthma	
Genes related to asthma and BMI	PRKCA, LEP, ADRB3 genes	Unknown	(119,122,123)
Loci involved in obese asthmatic children	ADRB2, TNF, LTA4H, GNPDA2 and ROBO1	Unknown	(119,124)

BMI, body mass index; HFD, high-fat diet; NR3C1, nuclear receptor subfamily 3 group C member 1; TNF, tumor necrosis factor; CHI3L1, chitinase-3-like 1 protein; ADRB, adrenoceptor β ; PRKCA, protein kinase α ; LEP, leptin; LTA4H, leukotriene A4 hydrolase; GNPDA2, glucosamine-6-phosphate deaminase 2; ROBO1, roundabout guidance receptor 1.

The glucocorticoid receptors encoded by NR3C1 may regulate airway inflammations, while TNF- α induces immune-inflammatory responses (123). Furthermore, an HFD upregulates the expression levels of chitinase-3-like protein 1 gene, whose expressed products are associated with obesity and asthma (124). In addition, the protein kinase α , leptin and ADRB3 genes have been found to be related to asthma and BMI (122,125,126). Furthermore, several loci, including ADRB2, TNF, leukotriene A4 hydrolase, glucosamine-6-phosphate deaminase 2 and roundabout guidance receptor 1, have been implicated in the pathogenesis of obese asthma in children (121,127).

Epigenetic mechanisms lead to heritable changes in the function of genes without altering the DNA sequence, which may be caused by environmental changes and dietary intake (128,129). Of note, prenatal and early-life environmental exposures have been reported to affect the risk of asthma and obesity in the adult stage epigenetically (128,130).

Histone modification, as one of the epigenetic mechanisms, is coordinated by histone acetyltransferases and histone deacetylases (HDACs), which comprise 11 classic subtypes, HDAC1-HDAC11. Inflammation of the airways and metabolic disorders linked to obesity may both be accompanied by HDAC9 expression. Studies have demonstrated that increased HDAC9 levels lead to impaired adipocyte differentiation induced by an HFD, and inhibiting the HDAC9 gene improves adipocyte differentiation and systemic metabolism, bringing about weight loss and increased sensitivity to glucose and insulin (131) with suppressed airway inflammation (25). Furthermore, SCFAs acts as an HDAC inhibitor, which may suppress inflammation by inhibiting the NF- κ B signaling pathway (132). Patients with asthma who have reduced HDAC2 levels are less responsive to glucocorticoid therapy (133).

DNA methylation, as one of the epigenetic mechanisms, may inhibit the promoter of genes encoding molecules in obese asthmatic children, including C-C motif chemokine ligand 5, IL-2 receptor α and T-box 21. Increased methylation is also

observed at the low-affinity receptor for IgE (Fc fragment of IgE receptor II) and the transforming growth factor β 1 gene (134).

In terms of genetic aspects, although the knowledge regarding the connection between obesity and asthma remains insufficient, genetic factors may have a potential effect on the morbidities of both asthma and obesity.

4. Potential treatments

The investigation of inflammatory mechanisms in obesity-related asthma is of significant importance for the advancement of clinical treatments. A comprehensive understanding of specific pathways involved in inflammation and targeting critical factors such as adipokines, gut microbiota and genes that contribute to immunological inflammatory response may facilitate clinical trials aimed at optimizing asthma therapies and prevention. Efficient therapies available for obese patients with asthma are currently under investigation. The effectiveness of weight loss has been demonstrated, while certain medications targeting the immune response in obese patients with asthma are also being further explored.

Weight loss. Weight loss accomplished through dietary adjustments, lifestyle interventions, medication applications, or bariatric surgery may markedly improve asthma outcomes (135-142). For obese individuals, improvements in asthma control, lung function and overall quality of life have been found after losing weight, with a trial revealing that obese individuals who lose at least 10% of their body weight may experience a meaningful improvement of clinical symptoms (137). Except for the mechanical effect of weight loss on improving lung function, its effects on the immune-metabolic route of asthma remain unclear.

Diet-induced weight loss may reduce airway inflammation with suppressed AHR (135). The crucial role of TNF- α as a mediator connecting asthma and obesity was also detected in mouse models (138). However, the heterogeneous results

of human studies suggested that the role of weight loss was more complex. Although marked clinical improvements in asthma control were observed, the levels of inflammation were not altered in obese asthmatic children after dietary-induced weight loss (139). A weight-loss program combining dietary and weight-loss medicine (sibutramine or orlistat) intake also revealed marked clinical improvements but without improvements in airway inflammation or bronchial reactivity (140). However, markedly improved clinical symptoms and life quality were found in adults who lost weight through comprehensive intervention of dietary restriction and exercise, while decreased airway inflammation was also observed with improved neutrophilic, eosinophilic and vitamin D levels, which differed from the unaltered inflammation in the aforementioned studies (71,141). Bariatric surgical treatments have been demonstrated to improve asthma outcomes as well, explained by improved small airway function and decreased systemic inflammation (136), as well as reduced metabolic inflammation, improved AHR and adjusted T-cell differentiation, which is involved in asthma pathogenesis (142). In obese mice, bariatric surgery and dietary-induced weight loss had equivalent effects in reducing the elevated AHR (135). These findings suggest that weight loss may be a potential therapeutic and daily management strategy for obese asthma patients, although its anti-inflammatory effect remains uncertain and requires further validation in human studies.

Medications. Medications aimed at regulating the abnormal immune responses in obese patients with asthma are currently at the exploratory stage, with a series of medications being potential treatments.

Celastrol is a natural bioactive molecule and has been found to have an anti-inflammatory effect to reduce AHR in allergic asthma, with a reduction in Th17 mRNA expression in mouse models (143,144). Since the Notch signaling pathway is involved in allergic airway inflammation and metabolism (145,146), γ -secretase inhibitors that can block the signaling pathway have been found to decrease the Th17 response and AHR in mice (147). C-X-C motif chemokine receptor 2 antagonist (SCH527123) is a small-molecule drug for non-type 2 asthma that has been revealed to markedly reduce neutrophil levels and improve asthma symptoms (148). However, it does not improve the clinical outcome of patients with refractory asthma (148,149) and its effect in obese patients with asthma remains unclarified. Certain medications at off-label dosages, including macrolides, statins and low-dose theophylline, may have a potential effect on non-type 2 asthma. Azithromycin can reduce asthma attacks and airway inflammation in patients with non-eosinophilic asthma (150,151). Statins, which have an immunomodulatory effect (152), may reduce hospitalization and restore the glucocorticoid sensitivity of patients with asthma (153), while their effectiveness in obese patients with asthma still requires further verification.

Glucocorticoids may inhibit the expression of pro-inflammatory genes, partly through their negative regulation of MAPK signaling pathways (154). Proinflammatory environments characterized by cytokines such as IL-1, IL-6 and TNF- α are observed in obese individuals and these are regulated by p38 MAPK or are its potential regulators, and thus, may alter glucocorticoid responses in obese patients with asthma (154). TNF- α expression has been reported to increase as the BMI

increases in patients with asthma, implying its potential role in interfering with the process of the glucocorticoid response in obese or overweight individuals with asthma (52). Monoclonal antibodies (mabs) against IL-17 or TNF- α may act on neutrophilic inflammation and restore glucocorticoid sensitivity in mouse models (155). However, clinical trials on brodalumab have provided disappointing results (156), and whether TNF- α mab improves glucocorticoid sensitivity in obese asthmatic patients remains unclear.

Insulin resistance may lead to metabolic syndrome and type 2 diabetes (157). As an important comorbidity of obesity-related asthma, insulin resistance is closely related to asthma development and exacerbation (21,158). Therefore, treatments targeting the metabolic process are critical for asthma control. Certain therapies to improve insulin resistance, such as metformin and sulfonylureas, have been found to improve asthma symptoms (159,160). In addition, glucagon-like peptide 1 receptor (GLP-1R) agonists, as diabetes medications, may raise insulin and inhibit glucagon secretion, as well as promote weight loss by delaying gastric emptying and increasing satiety (161), markedly inhibit airway inflammation and reduce airway eosinophilia, mucus production and AHR (162,163), suggesting their potential therapeutic implications for obesity-related asthma. Applications of GLP-1R agonists in patients with asthma combined with type 2 diabetes reduced the frequency of asthma exacerbations (164), implying their potential role in treating obesity-related asthma associated with metabolic dysfunction.

The aforementioned studies revealed potential methods for obesity-related asthma treatment, which still need to be substantiated by further studies. In addition, through analysis of gene expression, asthma phenotypes and endotypes associated with obesity may be further differentiated at the molecular level (6,165) and more corresponding phenotypic biomarkers may be found, thus contributing to finding possible methods for the effective treatment of obesity-related asthma.

5. Conclusions

Patients with obesity-related asthma exhibit inflammatory dysregulation, which differs from ordinary patients with asthma, and this may partly explain the clinical characteristics of obesity-related asthma in epidemiological studies, including severe asthma symptoms, difficulty in controlling symptoms and obvious resistance to conventional drugs such as glucocorticoids. However, numerous epidemiological aspects in this field remain unclear, particularly the correlation between asthma related to obesity and factors such as age, gender and BMI.

Metabolic disorders may hinder airway function in obese individuals through various mechanisms. Based on the present review, various factors such as oxidative stress, mitochondrial dysfunction, genetics and epigenetics related to the obese state may have impacts on asthma inflammation. In patients with obesity-related asthma, macrophages, lymphocytes, intestinal flora and certain adipokines produced by adipose tissue are also strongly linked to the immunological response through inhibiting the anti-inflammatory effect, activating multiple inflammatory signaling pathways and secreting various pro-inflammatory mediators and chemokines. In addition, genetic factors may potentially affect both asthma and obesity morbidity, including the genes ADRB2, NR3C1 and TNF- α .

Based on these findings and hypotheses, directions for future exploration are provided. Aiming at the special non-type 2 inflammatory types and inflammatory factors that are different between obesity-related asthma and ordinary asthma, the pathological process of inflammation and the mechanism of drug resistance will be further clarified by future studies, providing insightful targets and ideas for the management of obesity-related asthma. Furthermore, the role of various adipokines and genetic factors in the inflammatory process of asthma has not been fully elucidated, which may be expected to provide potential targets for the treatment of asthma in obese individuals through further research.

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Authors' contributions

ZQ, CH and YC conceived and designed the review. ZQ, CH, HY, JL, DL and YW wrote the manuscript and prepared the figures. ZQ, HY, DL and YC performed the literature search. JL, DL and YW critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript. All authors are responsible for all aspects of the work and approve the submission in its current form. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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