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Unraveling the Interrelationship of Microbiota, Inflammation and Obesity: Implications for the Pathophysiology of Asthma Endotypes

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Abstract: *Asthma is a multifaceted ailment characterized by fluctuating respiratory symptoms and variable airflow constriction. Traditionally, treatments focused on symptom management, universally applicable to all asthma types. Increased understanding has led to the classification of two major asthma endotypes: T helper type 2 (Th2) cell-high asthma, marked by type 2 cytokines, eosinophilic and allergic inflammation, and immunoglobulin E (IgE) synthesis; and Th2-low endotype, characterized by neutrophilic and systemic inflammation, associated with obesity and corticosteroid resistance. Though the pathogenesis of asthma remains incompletely understood, increasing evidence suggests a link between asthma and the interplay of "inflammation, obesity, and microbiota." The NF-κB and NLRP3 signal pathways play pivotal roles in the pathophysiological mechanisms of both asthma endotypes. Obesity and dysbiosis exacerbate systemic inflammation, particularly in relation to the Th2-low endotype. Future asthma treatments hold promises by targeting the underlying pathophysiology and personalizing interventions according to the specific endotypes. This review provides a synthesis of current research exploring the interconnected roles of inflammation, obesity, and the microbiota in asthma pathophysiology. However, further investigation is warranted to deepen our understanding and optimize therapeutic interventions for asthma management.*

Keywords: *Asthma, Endotypes, Phenotypes, Microbiota, Dysbiosis, Inflammation, Obesity, Immune system, Eosinophilic, Neutrophilic*

1. Introduction

Asthma presents as a multifaceted ailment characterized by fluctuating respiratory symptoms and variable airflow constriction. The manifestations are nonspecific in nature and encompass wheezing, dyspnea, thoracic constriction, and coughing [1]. Asthma manifests diverse phenotypes and endotypes, with phenotypes representing discernible attributes associated with triggering factors, such as atopic versus intrinsic, and the timing of onset, such as early-onset versus late-onset. On the other hand, endotypes define subgroups based on the underlying pathophysiology involved, for example, the involvement of T helper type 2 (Th2) cells. Th2-high asthma demonstrates distinctive attributes including eosinophilic inflammation and allergic sensitization mediated by Th2 cells [1–3]. In contrast, Th2-low asthma is typified by neutrophilic inflammation and non-atopic reactions mediated by T helper type 1 and 17 cells. Th2-low endotype asthma is often overlapped with the phenotype of obesity adult asthma, characterized by neutrophilic and systematic inflammation mediated by cytokines related to Th1 and Th17 cells lineage [4,5].

Until recent years, treatments have been universal for all types of asthma. However, responses to treatment have been varied, with an estimate 10% of all patients with asthma experiencing severe uncontrolled asthma. Defining asthma into endotypes by molecular characteristics is important for asthma control, by applying personalized therapeutic and prognostic intervention [4]. The current objective in the management of asthma is to attain optimal control by mitigating the risks associated with asthma-related mortality, exacerbations, airway impairment, and adverse effects of medication [6]. The Global Initiatives for Asthma (GINA) revised its guidelines in 2019, incorporating the pivotal role of anti-inflammatory reliever therapy across all levels of asthma severity, thereby emphasizing its significance in disease management. Inhaled corticosteroids are recommended as the reliever of starting

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treatment to all asthmatic patients to reduce the risk of serious exacerbation [6]. Clinically, a combination of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA e.g. Formoterol) and oral medication (e.g. theophylline) are mainstay of asthma medication as a step-up treatment to improve long term symptom control [1,7]. In addition, certain environmental control measures can reduce asthma exacerbations by avoiding airborne allergens. However, none of the available treatment options address the underlying condition of asthma [8], and corticosteroid resistance is common in a subgroup of severe asthma phenotype.

Although the pathogenesis of asthma is yet to be fully elucidated, growing evidence suggests an association between asthma and the interaction of the "inflammation, obesity and microbiota" triad. Various pathways of inflammation are implicated in different phenotypes of asthma [9,10]. Previously, asthma was attributed to its nature as a chronic inflammatory respiratory disorder marked by the presence of type 2 cytokines, namely interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). These cytokines are responsible for instigating airway eosinophilia, excessive mucus production, airway hyperresponsiveness (AHR), and immunoglobulin E (IgE) synthesis. However, contemporary understanding has revealed that Th2-high eosinophilic asthma represents just one endotype, and merely half of asthma patients exhibit indications of an amplified Type 2 response. Alternatively, Th2-low asthma exhibits distinct immuno-logical characteristics, such as airway neutrophilia, systemic inflammation linked to obesity, or, in some cases, signs of immune activation [11]. Th2-low asthma frequently manifests in various phenotypes, including obesity-related asthma, neutrophilic asthma, and paucigranulocytic asthma, all of which are linked to severe, inadequately controlled asthma [12]. A causal relationship between dysbiosis and chronic inflammation has been suggested [13]. Recent research has shown that both gut and airway microbiota compositions are associated with asthma. The concept of the gut-lung axis has been introduced in recent years, which provides a new perspective on the risks of developing and exacerbating asthma [14]. The mode of birth, feeding practices, and use of antibiotics can alter the microbiota and increase the risk of developing and exacerbating asthma. The microbiota composition and metabolites of obese individuals with asthma are distinct from those of normal-weight individuals with or without asthma. Moreover, findings from both animal studies and clinical trials have suggested the efficacy of microbiota transfer, probiotics, and prebiotics in addressing obesity concerns, thereby indicating a plausible etiological connection between gut microbiota and obesity [15]. Notably, obesity is correlated with heightened asthma symptom severity, suboptimal disease control, and escalated medication usage. Epidemiological investigations have consistently revealed a substantial correlation between obesity and the incidence of asthma. Adipose tissue releases inflammatory adipokines, which are linked to asthma. Conversely, weight loss interventions have been shown to improve asthma morbidity in a dose-dependent manner.

Despite an accumulating body of both mechanistic and clinical research on asthma, a few knowledge gaps are still blocking our odyssey to find the most effective dietary and nutrition intervention for asthma. For example, although several preclinical studies explored the relationship between the "inflammation, obesity and microbiota" triad and asthma, few studies focused on the interlink of these mechanisms with different endotypes of asthma. The latest understanding on the pathological mechanisms of asthma has not been fully translated into clinical studies either.

This review will summarize the pathological relationship between asthma and the etiologically related triad of "inflammation, obesity and microbiota".

2. Potential Underlying Mechanisms

Asthma is a multifaceted ailment and the mechanisms underlying its pathogenesis remains poorly understood. However, mounting evidence point to the interplay of inflammation [16,17], obesity [18,19], and microbiota [20,21] playing an important role in both inception and morbidity of asthma, across various endotypes and phenotypes. Understanding theses mechanisms which are summarized in Figure 1, may help to shed light on strategies for intervention to improve the outcomes for people with asthma.

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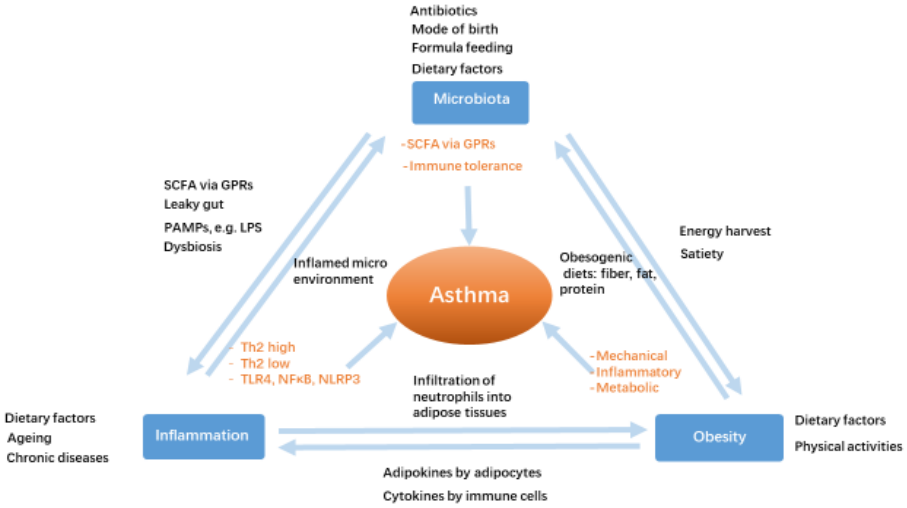

Figure 1: This illustrates the intricate relationships between inflammation, microbiota, obesity, and asthma, showcasing the bidirectional etiological pathways that impact the development and severity of asthma. Multiple interconnected pathways contribute to this intricate relationship. One such pathway involves Toll-like receptor (TLR)-mediated NLRP3 inflammation signaling, which plays a pivotal role in mediating both the Th2 high and Th2-low asthma phenotypes. The Th2-high phenotype is characterized by heightened eosinophilia, while the Th2-low phenotype is associated with neutrophilia. Dysbiosis disrupts the production of short-chain fatty acid (SCFA)-mediated anti-inflammatory cytokine IL10, consequently compromising immune tolerance during early life. Adipose tissues associated with obesity exert mechanical pressure on lung function. These tissues also secrete leptins, which mediate airway inflammation and metainflammation, further exacerbating the impact of obesity on the respiratory system.

2.1. Inflammation

The involvement of inflammation in the pathophysiology of asthma, characterized by airway inflammation and AHR, has been firmly established [22]. Effective asthma management mainly involves anti-inflammatory treatments [23]. However, while air-way inflammation in asthma is widely recognized, systematic inflammation in asthma has only recently gained attention. In individuals with asthma, particularly the severe phenotype, systemic inflammation increases with neutrophilic airway inflammation, leading to poor clinical outcomes [24,25]. Inflammation is an immune mechanism for defending against infection and promoting tissue repairs. This tightly regulated and evolutionarily conserved inflammatory response typically resolves itself upon eradication of infections and harmful agents under normal circumstances. However, dysregulation of this process often leads to chronic inflammation, intricately intertwined with the pathogenesis of numerous chronic diseases, encompassing asthma, chronic obstructive pulmonary disease, diabetes, metabolic syndrome, cardiovascular disease, cancer, and autoimmune disorders [26].

Inflammation encompasses a comprehensive framework comprising four essential constituents: the inducers of inflammation, the sensors or receptors responsible for its detection, the mediators, including cytokines and interferons, induced by these receptors, and the specific tissues targeted by these inflammatory mediators [27]. Inflammatory inducers comprise pathogen-associated molecular patterns (PAMPs), integral components of microorganisms, as well as damage-associated molecular patterns (DAMPS), originating from cellular debris caused by injury. Either PAMPs or DAMPs can initiate the inflammatory response of the innate immune system by activating pattern recognition receptors (PRRs), acting as the sentinel sensors of inflammation. Important classes of PRR families, comprise the Toll like receptors (TLRs) and the nucleotide-binding oligomerization domain, leucine-rich repeats containing receptors (NLRs), among others. TLR2 and TLR4 are extracellular PRRs situated on the cellular surface membrane, predominantly recognize microbial products, PAMPs. Ligating TLR2 or TLR4 activates the nuclear factor kappa B (NF-κB), a redox-sensitive transcription factor, through the MyD88-dependent pathway, resulting in the expression of cytokines, chemokines and other inflammatory mediators [28]. NOD-like Receptor Family Pyrin Domain Containing 3 (NLRP3) serves as an intracellular PRR capable of discerning both PAMPs and DAMPs. NF-κB primes the NLRP3-inflammasome for activation. The formation of the NLRP3 inflammasome precipitates the release of pro-inflammatory cytokines, such as

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interleukin-1β (IL-1β) and interleukin-18(IL-18). In murine models, IL-18 has been shown to induce a Th2 cell-mediated response, whereas inhibition of NLRP3 attenuates the systemic inflammatory response syndrome [29]. NLRP3 itself plays immune system–polarizing roles and is implicated in the pathophysiology of both Th2-high and Th2-low asthma endotypes.

The Th2-high endotype was formerly referred to as eosinophilic asthma due to the prevalence of eosinophilia in this asthma subgroup. Th2 cells secrete cytokines, such as IL-4, IL-5, and IL-13, which stimulate type 2 inflammation, as evidenced by elevated levels of IgE and eosinophils. Inflammation of Th2-high endotype is mediated by immune cells, including Th2 cells, eosinophils, mast cells, basophils, group 2 innate lymphoid cells (ILC2s) and IgE-producing B cells [9]. Although NLRP3 is primarily located in the cytoplasm of Th1 cells, it can be found in the nucleus of Th2 and Th17 cells, where it assumes the role of a transcription factor, operating independently from the inflammasome complex, in the presence of the cofactor IFR4. This process promotes IL-4 production, which in turn induces differentiation and expansion of Th2 cytokine-producing innate cells, forming the basis of Th2-high endotype asthma [30]. Notably, in a murine model induced by ovalbumin (OVA), the absence of NLRP3 in mice resulted in diminished levels of IL-4 and IL-5 within the pulmonary system, along with a concomitant reduction in eosinophil presence and mucus production [31]. These experimental findings implicate the activation of NLRP3 as a pivotal determinant in the pathogenesis of asthma [32]. Prolonged activation of NLRP3 by inhaled irritants and/or environmental allergens can result in severe pulmonary inflammation and exacerbation of asthma symptoms. It is noteworthy that the administration of NLRP3 inhibitors in asthma models can control AHR and pulmonary inflammation [32]. An in vitro study has reported that dust mite allergens could incite activation of the NF-κB/NLRP3 inflammatory pathway within bronchial epithelial cells sourced from individuals diagnosed with allergic asthma. NF-κB assumes a prominent role in severe asthma characterized by eosinophilic inflammation [33].

While considerable research has been dedicated to investigating the Th2-high endotype of asthma, which manifests as type 2 inflammation culminating in pulmonary and airway inflammation, the pathophysiology of Th2-low endotype, characterized by type 1 inflammation, remains unclear. Th2-low asthma endotype is characterized by the absence of type 2 biomarkers, including eosinophils and IgE, while featuring a prevailing abundance of Th17 cells and neutrophils within the airway milieu [35]. Emerging evidence substantiates the involvement of Th17 cells in the pathogenesis of Th2-low asthma [32]. Notably, within the lungs of individuals with severe asthma, there exists an upregulation of Th17 cells alongside heightened expression of IL-17A, which orchestrates neutrophil recruitment to the lung. While steroids, such as dexamethasone, can inhibit cytokine production by Th2 cells, their efficacy against Th17 cells remains limited, thereby proposing a plausible association between Th17 cells and steroid-resistant asthma [34]. In a mouse model simulating steroid-insensitive airway inflammation, IL-17 directly induces contraction of smooth muscle cells [35]. In an asthmatic patient cohort investigation, it was found that the expression of Th2 and Th17 genes were mutually exclusive, and no patient had high levels of both Th2 and Th17 cells, which suggests an inherent reciprocal relationship between these distinct cellular populations that correspond to the Th2-high and Th2-low asthma endotypes, respectively.

Remarkably, the neutralization of Th2-related cytokines, such as IL-4 and/or IL-13, in in vitro settings resulted in an augmented presence of Th17 cells alongside the onset of neutrophilic inflammation within the pulmonary milieu. This proclivity toward neutrophilic inflammation is recognized as a characteristic hallmark of the steroid-resistant severe asthma phenotype [36]. Despite the reciprocal relationship between Th2 and Th17 cells, both eosinophils and neutrophils can be present in excessive amounts in the airways of individuals afflicted with severe asthma [37]. Furthermore, inhibiting the nuclear receptor RORγt can simultaneously reduce Th17 and Th2 cell responses within the airway [38]. The activation of NLRP3 inflammasome induce polarization of Th17 cells and was correlated with serum concentration of IL-17 [39]. Knockdown of NLRP3 or inhibition of CAPAPAS-1 or IL1 receptor suppresses Th17 differentiation [40]. The reduction of reactive oxygen species (ROS) levels exerts a consequential impact on NLRP3 inflammasome activation, resulting in diminished production of IL-1β and an abrogation of Th17 differentiation. These empirical findings collectively imply a pivotal role of the NLRP3 inflammasome in driving the pathogenic process of Th17 cell differentiation [41].

The activation of TLR4 signaling pathway in innate immune cells predominantly elicits the production of type 1 cytokines, thereby fostering the development of Th1/Th17 cell-mediated immunity. It is postulated that diminished TLR4 activation during early life hampers the maturation of Th1 immunity, consequently tipping the balance towards Th2 responses and rendering individuals more susceptible to allergic diseases [42]. Lipopolysaccharides (LPS) and saturated fats (SFA) are the two main agonists of TLR4, both of which are commonly found in Western diets that are high in SFA and refined carbohydrates but lack of fiber [43]. Reduction in saturated fat intake has been associated with

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an improvement in neutrophilic airway inflammation among men diagnosed with asthma [44]. Dietary fat requires chylomicrons as lipid proteins, which package intestinal LPS, a key component of Gram-negative bacteria, with triglyceride for circulation. Excessive refined carbohydrates, particularly sugar-sweetened beverages, have also been found to increase intestinal LPS and systemic LPS (endotoxins). Both saturated fats and refined carbohydrates are typical of Western diets.

The impact of endotoxin exposure on atopic asthma demonstrates a notable dependence on the timing of such exposure. The hygiene hypothesis derived from studies of children raised in rural communities, suggests that early-life endotoxin exposure might confer a protective effect against the development of atopic asthma [45]. In a murine model, LPS inhalation before exposure to antigen was found to impart a safe-guarding influence against the onset of asthma by modifying the microenvironment within the bronchioalveolar region. This regulatory mechanism encompasses the induction of intrinsic anti-allergic pathways, while concurrently modulating local factors that contribute to Th2-mediated allergic inflammation [46]. During the early stages of life, the influence of LPS exposure emerges as an additional consequential factor impacting TLR4-mediated Th2 response. Intriguingly, the exposure of newborn mice to LPS has been demonstrated to curtail airway inflammation, mitigate AHR, and suppress the expression of Th2 cytokines, while concurrently promoting the production of IL-10. These observations collectively suggest that exposure to LPS, particularly in association with the gut microbiota during the neonatal period, might confer a degree of tolerance towards environmental allergens [42]. Nevertheless, it is important to acknowledge that LPS exposure could potentially contribute to the manifestation of non-atopic respiratory disorders and potentially exacerbate existing asthma in affected individuals [47,48]. Timing and dosage of antigens in contact, either airway or systemic antigen contact, all induce different immune responses. It has been shown that while low dose of airway exposure to LPS triggered eosinophilic inflammation, high dose of LPS triggers Th1-mediated neutrophilia phenotype of asthma [42]. In a murine model, inhalation of low doses of antigens of LPS induced an allergic response with infiltration of both eosinophils and neutrophils, mucus secretion in airway, as mediated by increase in Th2 cytokines production and activation of TLR4 signaling pathway [49]. However, when mice were exposed to high dose of LPS, a distinct immunological profile emerges, with the induction of a Th1-associated response rather than a Th2 response. This results in airway neutrophilia without mucus secretion but with heightened production of IFN-γ. Importantly, irrespective of the LPS dose administered, a consistent upregulation of TLR4 expression is observed in alveolar macrophages within the lungs, indicating that the TLR4 inflammation signaling pathway may be involved in both Th2-high and Th1-low asthma endotypes [50]. Combining these findings, it can be inferred that low dose of potentially innocuous antigens, which may be associated with environmental endotoxin, can trigger allergic asthma in sensitized individuals, characterized by a Th2-high inflammatory response. Conversely, high doses of LPS antigens, which may be associated with systemic circulation, can trigger non-allergic asthma characterized by a Th2-low inflammatory response. Both inflammatory responses are mediated through the TLR signaling pathway. Future mechanistic and human studies are required to validate this hypothesis.

2.2. Obesity

The World Health Organization (WHO) has issued dietary guidelines for the management of healthy weight, yet obesity and its related diseases continue to represent a pandemic, with a rising incidence among both adults and children [51]. A prospective study on asthma showed that obesity affected 45% of children and 58% of adults with asthma [52]. Notably, it has been observed that adults with asthma who are classified as obese exhibit a heightened utilization of various asthma medications, such as β2-agonists and maintenance oral corticosteroids, than healthy-weight subjects, despite comparable pulmonary function. In addition, obese subjects received a significantly higher inhaled corticosteroid dose [53]. Moreover, uncontrolled asthma control and worse respiratory functions demonstrated a stronger association with abdominal obesity than BMI in adults [54].

The correlation between obesity and asthma is multifaceted. The relationship between obesity and asthma is partly underpinned by genetic factors. Genetic analysis of risk alleles for obesity suggest heightened adiposity may serve as a predisposing factor for the development of asthma, especially in childhood. In contrast, the reciprocal influence of asthma on adiposity accumulation appears to be less pronounced [55,56]. Besides genetic factors, various hypotheses have been put forward to unravel the mechanisms underlying the connection between the two, including the mechanical and immunological effects of obesity. Other possible explanations for the correlation between obesity and asthma include metabolic factors (e.g. insulin resistance), dietary factors (e.g., western-style diets), lifestyle factors (e.g., lack of physical activity), and chronic diseases such as sleep apnea and gastroesophageal reflux disease

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(GERD), which are often associated with obesity [57].

The mechanical hypothesis suggests that the presence of truncal adiposity, an inherent characteristic of obesity, exerts detrimental effects on various respiratory parameters, including functional residual capacity (FRC), residual volume (RV), and expiratory reserve volume (ERV). This reduction in pulmonary capacities consequently gives rise to breathing difficulties in individuals affected by obesity. The accumulation of adipose tissue, a hallmark consequence of obesity, imparts undue pressure upon the chest wall, thereby impeding the unrestricted movements of both the thoracic cage and diaphragm during the respiratory process [58]. Furthermore, the consequential reduction in cross-sectional area resulting from obesity has been postulated to potentially augment the contractility of airway smooth muscle [59].

According to the hypothesis of immunological factors, obesity represents a chronic low-grade inflammatory state that has been intricately linked to the development of asthma, thus exerting discernible effects on pulmonary function. Far from being a mere repository for excess energy intake, adipose tissue is an intricate and multifaceted endocrine organ that actively contributes to the balance of inflammation homeostasis [16]. Adipocytes secrete adipokines such as leptin, adiponectin, and resistin. Adiponectin has anti-inflammatory activities, while leptin has pro-inflammatory activities. Remarkably, leptin serves as a survival factor for both neutrophils and eosinophils, as evidenced by the presence of leptin surface receptors on these immune cells. Furthermore, in vitro studies have revealed that leptin significantly delays the programmed cell death of mature eosinophils and neutrophils, thereby resulting in a notable increase in their respective concentrations [60,61]. Leptin is therefore considered a pivotal inflammatory mediator in the intricate pathogenesis of asthma, rendering it a subject of considerable interest and investigation [62,63]. In airways of asthmatic patients, inflammatory leptin-producing monocytes accumulated in the airway [64], elevating Th2 and Th17 cytokine levels and favoring the expansion of Th17 cells while decreasing regulatory T (Treg) cells [65]. In a murine model, the administration of exogenous leptin through infusion yielded a direct causative effect on the increase in AHR and serum IgE levels [66]. In obese mice fed high-fat diets, blocking of IL-17 by antibodies not only abrogated inflammation and AHR but also increased the leptin/adiponectin ratio [67].

Leptin also promotes airway inflammation by upregulating mitochondrial ROS, thereby triggering the activation of the NLRP3 inflammation pathway [68]. Asthmatic individuals with a healthy BMI exposed to over-nutrition exhibited discernible NLRP3-mediated airway inflammation. Notably, this effect was even more pronounced in obese individuals with asthma, leading to a significant elevation in the levels of IL-5, IL-1β, and sputum neutrophils. This observation underscores the potential therapeutic value of targeting the inflammasome as a viable approach in managing obesity-related asthma [16].

In humans, the precise role of leptin in the context of asthma remains incompletely elucidated. Levels of leptin demonstrate an association exclusively with overweight and obesity, irrespective of asthma status [69]. In children, leptin concentrations are higher in those with both obesity and asthma, and although BMI and leptin are predictive markers for severe asthma, leptin concentrations are higher in both obesity and asthma [70]. Furthermore, it has been revealed that levels of leptin and IL-10 increased in obese children with asthma, while adiponectin and tumor necrosis factor-α (TNF-α) exhibited a significantly higher expression in normal-weight children with asthma [71].

The relationship between adiponectin and asthma is still inconclusive, as some studies report contradictory findings [72]. Adiponectin is lower in obesity and inversely related to severe asthma [70]. An adiponectin analog has been shown to inhibit Th2/Th17-skewed immune polarization, thereby suppressing Th2 and Th17 dominant immune responses, and upregulating IL10 activities [73]. Although adiponectin is generally believed to have an anti-inflammatory effect and be protective against asthma [74], some evidence indicates that adiponectin level is inversely associated with spirometry in asthmatic patients. This observation implies that adiponectin may potentially aggravate asthma by virtue of its anti-Th1 inflammatory properties, thereby promoting enhanced Th2 differentiation and exacerbating allergic responses of greater severity [75]. Nonetheless, the precise role of adiponectin in asthma, particularly its impact on Th2 differentiation and allergic responses, necessitates further investigation in forthcoming studies.

Despite the pivotal role of atopic inflammation in the initiation of asthma, it is noteworthy that non-atopic inflammation, including the involvement of leptin and adiponectin, can exacerbate the severity of asthma in individuals who are overweight or obese [76]. Recent investigations, such as a meta-analysis conducted by Nyambuya et al., have highlighted contrasting immune responses mediated by T-helper cells in lean and obese children with asthma. Obesity has been found to skew the immune response towards a Th1 phenotype, deviating from the classical Th2-dominant endotype. Moreover, obesity-related inflammation has been associated with elevated Th1 and Th17 responses, accompanied by

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reduced Th2 and Treg cells [77]. This suggests that inflammation triggered by obesity is predominantly orchestrated by Th1 and Th17 cells, thereby implying a considerable overlap between the asthma phenotype associated with obesity and the Th2-low endotype. Based on the above findings, a treatment strategy targeting the Th2-low endotype and neutrophilia may yield better therapeutic results for the obesity phenotype of asthma.

2.3. Microbiota

The “Hygiene hypothesis”, proposed about 40 years ago, originated from the observation that early exposure to environmental conditions harboring a heightened bacterial burden correlated with a reduced susceptibility to the development of atopic asthma [45]. Mounting evidence suggests that only a limited window of opportunity is available in the early stages of life when “normal microbiota” could educate the immune system to develop tolerance and avoid developing atopic diseases later in life. While this phenomenon of “normal” bacterial colonization is commonly referred to as symbiosis, the disruption of microbiota communities by environmental factors is called dysbiosis [78]. Divergences in gut microbiota exist between children afflicted with asthma and their healthy counterparts [79]. Observation studies have illuminated that key factors shaping the composition of gut microbiota in infants encompass the delivery mode, lactation type, gestational age, infant hospitalization, and the employment of antibiotics in infants. Of particular interest, term infants born through vaginal delivery in a domestic setting and exclusively nurtured through breastfeeding exhibited a prevailing presence of gut microbiota deemed "beneficial" [80].

The mode of delivery exerts a profound impact on the intricate arrangement of the gut microbiota during the neonatal phase, persisting into early infancy, thereby impinging upon the maturation of the immune system and the subsequent proclivity toward childhood allergies, asthma, and autoimmune disorders [81]. Analysis of the complete genomes of bacterial strains derived from neonates born via cesarean section revealed the presence of virulence determinants and clinically significant antimicrobial resistance within opportunistic pathogens, thereby potentially heightening an individual's vulnerability to opportunistic infections [82]. Neonates delivered through the vaginal route acquired a microbiota akin to their maternal vaginal microbiota, characterized by the predominance of *Lactobacillus*, *Prevotella*, or *Sneathia* spp. Conversely, infants born via cesarean section harbored microbiota reminiscent of those inhabiting the skin surface, marked by the prevalence of *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp [83]. A meta-analysis underscored the association between cesarean delivery and a heightened 20% risk of asthma development during childhood [84].

While the mode of delivery has paramount influence over the makeup of the intestinal microbiota during the nascent stages of life, the subsequent trajectory of microbiota is additionally shaped by the modality of lactation. Breastfed infants exhibit a heightened prevalence of beneficial bacteria, such as *bifidobacteria* and *lactobacilli*, while formula-fed infants exhibit diminished levels of *bifidobacteria* [85]. The "bifidogenic effect" of human milk can be attributed to its prebiotic attributes, encompassing a diminished concentration of proteins and phosphates, as well as the presence of lactoferrin, lactose, nucleotides, and oligosaccharides [85]. Breast milk contains immunoglobulin A (IgA), which attaches to pathogens and prevent them from adhering to an infant’s cells, reducing the risk of infection. Additionally, breast milk harbors an array of antimicrobial substances, such as lysozyme, lactoferrin, and human milk oligosaccharides (HMOs), which can prevent the adhesion of pathogens and viruses to an infant's mucous membranes, thereby preventing infection and fostering the proliferation of beneficial microbiota. HMOs, as prebiotics, undergo unabsorbed transit through the small intestine, ultimately reaching the large intestine, where they engender the proliferation of beneficial bacteria that can metabolize HMOs and enhancing the production of short-chain fatty acids (SCFA) [78]. Two comprehensive meta-analysis studies, taking into account 117 and 42 studies, respectively, underscore the link between the duration and exclusivity of breastfeeding and a diminished risk of childhood asthma, with the strongest association observed during the early years [86,87].

It was found that the fecal microbiota of infants subsequent to the commencement of complementary food ingestion differs from that before weaning [88]. However, the composition of the microbiota was most significantly influenced by the cessation of breastfeeding rather than the introduction of complementary food. Between 9 to 18 months of age, a positive correlation emerged, linking the augmentation of body mass index with the heightened presence of SCFA-generating clostridia, the *Clostridium leptum* group, and *Eubacterium hallii* [89].

The utilization of antibiotics in infancy revealed a marked correlation with diminished quantities of bifidobacteria and *Bacteroides* in the microbiota [80]. Early life administration of antibiotics engendered

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an augmented susceptibility to atopic conditions and metabolic diseases during subsequent stages of life [90]. In particular, the administration of antibiotics within the initial two years of life emerged as a discernible risk factor for the development of present-day asthma, atopic dermatitis, and allergic rhinitis in children reaching the age of five [91]. The administration of antibiotics during the first year of life exhibited a significant association with developing asthma throughout lifetime [92].

A prospective cohort study conducted in Canada by Patrick et al. suggested that the decline in pediatric asthma prevalence observed in the country could potentially stem from an unanticipated benefit of the exercise of judicious antibiotic administration during infancy [93]. It was found that children administered with antibiotics had a higher incidence of asthma. More specifically, the proportion of children who developed asthma without antibiotic exposure and with exposure to 1, 2, or 3 courses of antibiotics were 5.2%, 8.1%, 10.2%, and 17.6%, respectively. A clear positive correlation was found between propensity for asthma development before the age of 5 and the dosage of antibiotics prescribed before the age of 1. Notably, for every 10% increment in the prescribed antibiotic dosage, the probability of asthma incidence escalated by a substantial 24%. A population based birth cohort study in Finland also found a similar dose dependent effect of antibiotics administered in the first year of life on risk of asthma [94]. Another retrospective study undertaken in the United States unearthed that children subjected to antibiotic regimens were burdened with a 3.5-fold elevated risk of asthma development, alongside a 2.4-fold heightened proneness to allergic rhinitis, relative to their antibiotic untouched counterparts [92]. Antibiotic exposure in the ages of 2 to 7 years can alter the microbiota for more than two years, increasing the risk of not only asthma but also antibiotic associated weight gain [95].

SCFA produced by the gut microbiota have been reported to have a protective role against asthma [96]. Mice on a high-fiber diet had increased systematic SCFA and decreased allergic inflammation in the lungs. The protective effect of SCFA was mediated through the G-protein-coupled receptor (GPR), particularly GPR41, which is an extracellular receptor for SCFA expressed in immune cells [97]. A similar effect of SCFA was found on inflammation of humans with asthma [98].

The concept of gut-lung axis has emerged to refer to the relationship between alterations of microbiota composition in intestine and their profound repercussions on pulmonary disease. While the exact mechanisms underlying the dialogue between the gut and lungs are yet to be fully elucidated, bacterial metabolites originating within the gut are believed to permeate into the circulatory system to influence the migration of immune cells in the airway. Immune cells in airways could absorb signals from gut microbiota and form a local cytokine microenvironment remotely [12,78]. Healthy lungs are not sterile either and microbiota in airways are related to the development, phenotypes and severity of asthma [78]. It was consistently found that higher representation of a few genera, including *Moraxella*, *Haemophilus*, *Streptococcus* and *Staphylococcus*, in the airways are associated with the risk of asthma onset and severity [99–105]. In vitro, *Moraxella catarrhalis* collected from nasal airway of asthmatic children exhibited a markedly heightened propensity to instigate detrimental epithelial impairment and the expression of pivotal inflammatory cytokines, including IL-33 and IL-8, both of which are linked to the intricate pathophysiology of pediatric asthma, compared to other prevalent nasal bacteria [105].

The impact of antibiotics on asthma is not limited to the gut microbiota, as they can also affect the microbiota in the nasal airway. Antibiotic treatment in children during their first year of life had a dose-dependent effect on the nasal airway microbiota patterns during the first 2 years of life [94]. A prospective study involving a cohort of 234 children revealed that the administration of antibiotics disrupted nasopharyngeal microbiome, which led to increased severity of lower respiratory infections, concomitant with an augmented proclivity for the development of asthma [106].

The composition of microbiota can tilt T cells to mature in different direction and assume paramount importance in polarizing asthma endotypes [107]. Germ-free mice developed Th2-mediated allergic responses, characterized by heightened levels of IgE and IL-4, but abrogated Th1-mediated immune responses, after OVA challenge. Restoring the intestinal microbiota of germ-free mice by *B. infantis* protects them from developing Th2-medated allergic responses but, this is only effective when such restoration is performed in their neonatal stage [108]. Similarly, mice treated with early-life antibiotics exhibit Th2-mediated allergic airway response after antigen challenges [109,110]. On the other hand, in an OVA-induced asthma model, mice infected with *H.influenza* developed a Th2-low endotype-like allergic airway affliction, characterized by heightened neutrophilic inflammation and bolstered IL-17 immune responses, but suppressed eosinophilic inflammation [111]. Collectively, these studies underpin the crucial role of microbiota in the pathophysiological mechanisms underlying the susceptibility, severity, and endotypes of asthma.

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3. Interplay of Inflammation, Obesity and Microbiota, beyond Association

3.1. Obesity and Inflammation

Obesity represents a persistent and wide-ranging systemic inflammatory disease, marked by the accumulation of various deposits of adipose tissue across the entirety of the body, along with an elevation in the levels of cytokines within the circulatory system. Adipose tissue can be categorized into white adipose tissue (WAT), brown adipose tissue (BAT), and brown-like adipose tissue, with WAT primarily serving as the principal reservoir for surplus energy storage in the triglyceride format [112].

3.1.1. Inflammatory Pathways in Obesity

A recent systematic review reported that individuals with asthma and obesity exhibit a distinct inflammatory profile characterized by an augmented presence of neutrophils in both sputum and systemic circulation, implying the presence of neutrophilic inflammation in both the airways and the overall system of asthmatic individuals with an obese phenotype [113]. The obese asthma phenotype is potentially driven by systemic non-allergic inflammation, displaying a prevalent Th1 cell-mediated immune response characterized by elevated levels of interleukin-6 (IL-6), TNF-α, and interferon-gamma (IFN-γ) [62]. The escalation in cytokine concentrations may serve as the primary pathophysiological mechanism underlying the capacity of obesity to exacerbate inflammatory processes within the asthmatic airways. TNF, a pro-inflammatory cytokine, is expressed in human adipocytes. Kern et al. reported an affirmative correlation between TNF and the adiposity of subjects. Weight reduction could reduce TNF. It was observed that when weight was reduced by 26.6%, adipose TNF dropped to 58% of the level at baseline [114]. In another human study, volunteers significantly compromised their insulin sensitivity after infusion with the pro-inflammatory cytokine TNF, indicating the regulatory role played by TNF in the pathogenesis of insulin resistance, which is associated with obesity [115].

3.1.2. Inflammation as a Contributing Factor to Obesity

Metaflammation refers to a state of persistent, low-grade inflammation that emerges in the context of obesity, which alters metabolism [74]. In a murine study, adipose tissue displayed infiltration by neutrophils in response to a high-fat diet even before the onset of obesity [116]. Insulin resistance began to develop within three days of commencing the high-fat diet, coinciding with neutrophil infiltration into adipose tissue. Inhibiting such infiltration, impairment in hepatic insulin signaling was abrogated and the secretion of TNF-α by adipose tissues was attenuated [117]. Inflammation mediated by immune cells precedes the manifestation of metabolic disorders and obesity induced by high-fat diet [118]. Infusing LPS, an inflammation inducer, into mice fed a normal diet yields obesity and elicits metabolic responses bear some resemblance to those triggered by high-fat feeding. CD14 mutant mice, which lack an immune response to LPS to develop inflammation, display a protective effect against LPS infusion and high-fat diet-induced consequences, as demonstrated by their delayed development of most features of metabolic disorder and obesity, primarily due to their intact insulin sensitivity. In humans, 24 weeks of calorie-restricted anti-inflammatory diets (similar to Mediterranean diets), which lowered inflammatory markers, such as CRP, interleukin-6 (IL-6) and TNF-α, were capable of inducing a significant reduction in weight and adiposity [119]. The above evidence from both murine and human studies suggests a plausible causal connection between chronic inflammation and the development of metabolic disorders, specifically the promotion of obesity and the emergence of insulin resistance [120].

3.2. Microbiota and Obesity

Lower microbiota diversity is positively associated with obesity [121]. Up to 40% of overweight and obese patients, and up to 75% of severely obese patients exhibit low microbiota richness and dysbiosis [122]. Research on 64,580 hospitalized children revealed that those who had used antibiotics before the age of 2 had a higher probability of obesity, which further increased with the use of broad-spectrum antibiotics [123]. A Canadian study conducted in 2014 also revealed an increased likelihood of obesity development in children who had used antibiotics before the age of 1, as observed in the follow-up assessments conducted at 9 and 12 years of age [124].

3.2.1. Dysbiosis as a Potential Causal Factor for Obesity

Dysbiosis has been suggested as a possible cause of obesity, exerting its influence through mechanisms related to energy extraction and satiety regulation [125]. Experiments conducted on germ-free mice as well as preliminary evidence from human study support dysbiosis as a causal factor for obesity. Microbiota derived from obese mice exhibits an enhanced capacity to harvest energy from food,

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as evidenced by transplantation of fecal microbiota from obese mice to germ-free mice of lean phenotype resulted in a more pronounced induction of obesity compared to transplantation of microbiota sourced from lean donors [126]. Furthermore, when exposed to an identical high-fat diet, only the wild-type mice, but not germ-free mice, developed obesity [127]. In a human study, when microbiota from lean subjects were transferred to obese subjects with metabolic syndromes, insulin sensitivity improved. It was found the SCFA-producing bacteria, which have been shown to have a role in regulating satiety, of obese recipients increased after transplantation [128]. In an obese murine model, those subjected to a high-fat diet exhibited LPS levels that were up to threefold higher than those fed a normal chow. Injection of LPS into mice that were fed normal chow for 4 weeks resulted in inflammation, followed by obesity and insulin resistance [120].

3.2.2. Dysbiosis as a Contributor to Inflammation

Evidence of obesity causing dysbiosis is more elusive, as diet change is often involved in weight loss interventions, making it difficult to discern the independent effects of consuming healthy diet with restricted calories and adiposity reduction on the composition of microbiota. Microbiota change after bariatric surgery shed some light on impact of weight loss on dysbiosis [122]. A significant increase in microbiota diversity in obese subjects was observed in 3-12 months after Roux-en-Y gastric bypass (RYGB), a type of weight-loss surgery [129]. Despite gastric bypass improving dysbiosis, it failed to completely restore the diversity of microbiota of those who had very low microbiota richness at baseline, compared to lean subjects [130]. Bariatric surgery exhibits the capacity to alter the composition of the microbiota, as evidenced by multiple studies highlighting an increase in the *Proteobacteria* phylum following such surgical interventions, notably the gamma proteobacteria class [131]. Furthermore, it has been observed that post bariatric surgery, there is an augmentation in the abundance of *Akkermansia muciniphil* (*A. muciniphil*), which has been reported to have a counteractive effect on adiposity [132], and a protective effect on the inception of asthma and hyper-sensitivity of the airway [133,134]. Overall, weight loss induced by bariatric surgery could improve dysbiosis to certain extent, but the cofounding influence of healthy diets typically recommended after bariatric surgery cannot be excluded. A human intervention study showed that men with low microbiota diversity, as represented by "low gene content" of microbiomes, could increase their microbiota diversity after six weeks of caloric restriction, to nearly the same levels as observed in healthy control [135]. Interestingly, when comparing the effects of weight loss induced by bariatric surgery, specifically laparoscopic sleeve gastrectomy (LSG), and calorie restriction (CR) over the course of one year, distinct alterations in the composition of the gut microbiota were observed. Notably, bariatric surgery led to a notable increase in the abundance of *Bacteroidetes*, accompanied by a decline in *Firmicutes*. Conversely, the dietary intervention resulted in a reduction of *Bacteroidetes* in favor of *Firmicutes,* a decrease in the energy reabsorbing potential of the gut microbiota following bariatric surgery. However, both weight loss interventions, potentially due to the lack of dietary fiber, did not exhibit significant differences in fecal SCFA contents [136]. Obese adolescents on a 3-month program of calorie-restricted diets and increased exercise have their fecal LPS-generating *Entero-bacteriaceae* bacteria significantly decreased, particularly those whose lost weight [137]. As dietary factors exert a profound influence on the intestinal microbiota, regardless of weight loss, the mechanism by which obesity changes composition of microbiota may involve dietary components particular to the CR intervention chosen diet [138].

3.3. Microbiota and inflammation

3.3.1. Dysbiosis as a Contributor to Inflammation

Circulating levels of LPS is one of the key links between the gut microbiota and inflammation [139]. The gut microbiota regulates integrity of the intestinal mucosal barriers. Pathogens, xenobiotics and unhealthy food can cause dysfunction in gut permeability, leading to bacterial translocation into the bloodstream and the activation of immune-signaling pathways, resulting in a chronic, low-grade inflammatory response [138,140]. This phenomenon of increased intestinal permeability is also called "leaky gut syndrome". The metabolites produced by intestinal microbiota can be either anti-inflammatory or pro-inflammatory. SCFAs, such as butyrate, propionate, and acetate, are examples of anti-inflammatory bacterial metabolites. Upon binding to G-protein coupled receptors, SCFAs have the ability to diminish the production of neutrophils and macrophages and increase immunotolerence. In contrast, PAMPs and antigens are pro-inflammatory. LPS, a major type of PAMPs, is widely present in the intestine and is a cell wall component of gram-negative bacteria. When LPS is translocated into the circulation system, it binds to extracellular TLR4 and triggers immune signaling through NF-κB [140], resulting in a downstream inflammation cascade, including the activation of the pathway of the NLRP3 inflammasome, mediating the release of the pro-inflammatory cytokines such as IL-1β and IL-18 [141].

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IL-1β plays a pivotal role as a modulator in the context of asthmatic airway smooth muscle hyper-reactivity, primarily by activating eosinophils and inducing the excessive release of acetylcholine. Acetylcholine exerts its effects on the M3 receptor, which is closely associated with the contraction of airway smooth muscles and heightened mucus production [142]. IL-18 is another pro-inflammatory cytokine that can act as a cofactor in the maturation of Th2 cells, IgE production, and is also associated with the pathogenesis of asthma [143]. There were two pathways, by which LPS and other intestinal antigens could enter circulation: transcellular and paracellular pathways [144]. Chylomicrons induced by high-fat diets have a high affinity for LPS and can modulate transcellular translocation of intestinal LPS into circulation, independent of intestinal integrity. On the other hand, compromised intestinal barrier function may augment the paracellular translocation of LPS [145]. High-refined carbohydrate and high-fat diets are both independent factors that can cause impairment of the intestinal barrier and enhance paracellular translocation of LPS into circulation, resulting in systemic inflammation [146,147].

3.3.2. Inflammation as a Promoter of Dysbiosis

It is widely recognized that intestinal inflammation leads to disturbance of the gut microbiota [17]. Inflammatory stressors alter the microenvironment, which selects for the most adaptable microbiomes to thrive. These stressors include changes in nutrient sources, oxygen and iron availability, secretion of ROS and reactive nitrogen species (RNS) by immune cells, and the release of sialic acid by mucin2 (MUC2), a secretory protein abundantly found in the human gut. Notably, the emergence of *Enterobacteriaceae*, a group of Gram-negative bacteria that includes pathobionts like *E. coli*, *Salmonella*, *Klebsiella*, *Shigella*, and *Yersinia pestis*, has been closely associated with intestinal inflammation. As LPS, a cell wall component of *Enterobacteriacease*, is a potent PAMP promoting inflammatory responses, the bloom of *Enterobacteriacease* at the expenses of other commensal bacteria such as *Bacteroidia* and *Clostridia* is considered to be classical dysbiosis. For example, patients with Inflammatory Bowel Diseases (IBD) exhibit a higher prevalence of *Enterobacteriaceae*, including adherent invasive *E. coli* [148], suggesting that their growth is more likely a consequence rather than a cause of inflammation [17]. Inflammation also alters nutrient sources for gut bacteria. Damage to the mucosal epithelium due to inflammation results in shedding of deceased epithelial cells and a heightened level of phospholipids, including ethanolamine, derived from membrane of these deceased cells. Certain bacterial species can utilize ethanolamine as a source of carbon and nitrogen, thereby promoting the overgrowth of bacteria such as *Salmonella* and *Pseudomonas* [149]. Secretion of superoxide radicals, including nitric oxide (NO), is part of the inflammation process. The nitrate-rich microenvironment in inflammatory intestinal tissue favors the growth of *E.coli*, which is capable of nitrate respiration, but restricts the growth of obligate anaerobic bacteria such as *Bacteroidia* and *Clostridia* [150]. *Enterobacteriaceae* are facultative anaerobes that can adapt to oxygen availability in the intestine and obtain energy by switching between aerobic respiration and fermentation. A more aerobic microenvironment in the inflammatory intestine, due to higher blood flow and hemoglobin, favors the growth of *Enterobacteriaceae*, including *Salmonella* and *E.coli* [151]. Crucial to the maintenance of intestinal integrity and microbiome homeostasis is MUC2 [152]. During inflammation, the activation of NF-κB upregulates MUC2 expression. Sialic acid, one of the carbohydrates present in mucins, can be utilized by specific bacteria such as *E. coli*. Inflammatory processes lead to an upsurge in MUC2 production and sialidase activity, which facilitates the release of sialic acid from the intestinal tissue. This, in turn, promotes the proliferation of E. coli during inflammation [153]. Although an abundance of evidence supports the notion that local inflammation in intestine skews the microenvironment in favor of certain bacteria, specifically pathobiont species of *Enterobacteriaceae* resulting in dysbiosis, there remains insufficient evidence to suggest a direct impact of systemic inflammation on gut microbiota. While the studies above point to the mediating effect of inflammatory micro-environment on microbiota communities, the effect of systematic inflammation on microbiota remains to be determined.

4. Conclusion

The pathogenesis of asthma remains a subject of ongoing investigation, with several underlying mechanisms yet to be fully elucidated. Recent research has highlighted the intricate interplay between inflammation, obesity, and the microbiota in the context of asthma. Growing body of evidence has led to the identification of two major asthma endotypes: Th2-high asthma, characterized by type 2 cytokines, eosinophilic and allergic inflammation, and immunoglobulin E (IgE) synthesis; and the Th2-low endotype, characterized by neutrophilic and systemic inflammation, often associated with obesity and corticosteroid resistance. Importantly, the inflammatory pathways involved in these endotypes exhibit distinct features.

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Moving forward, the treatment of asthma should embrace a personalized approach, considering the individual patient's endotype. The intricate relationship among inflammation, obesity, and the microbiota underlining the pathophysiological mechanism of asthma support the notion that a comprehensive treatment strategy targeting obesity, systemic inflammation, and dysbiosis simultaneously may yield more favorable therapeutic outcomes for individuals with the Th2-low endotype, which is often associated with severe uncontrolled asthma. In this context, there is a need for future studies to explore human intervention trials in order to validate these promising therapeutic approaches. By understanding the underlying mechanisms and tailoring interventions accordingly, it is hoped that future treatments will yield improved outcomes for asthma patients.

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