Current Treatments and Advancements in Asthma Therapeutics

Anvi Shah

Abstract

Asthma is a prevalent respiratory condition affecting over 300 million people worldwide as of 2024, with substantial mortality rates each year. In 2019, there were 455,000 asthma-related deaths. Despite advances in patient care for asthma, there are still many asthma-related deaths occurring each year. Corticosteroids such as Flovent, Asmanex, and Qvar are the main form of medication to treat asthma, but users often experience adverse side effects like heart palpitations, dizziness, and chest pain. This makes it extremely hard for patients who are asked to take this medicine multiple times a day in order to treat their asthma.

Recent advancements in asthma therapeutics have led to the development of new, non-steroid-based treatments with fewer side effects and improved efficiency over the long term, with one linking asthma to gut health. Emerging research introduces the concept of the “gut-lung axis”, which implies that the gut and lung microbiomes influence each other. This means that the gut microbiome influences our immune system and can affect the severity of asthma and its symptoms.

This paper highlights the advancements in asthma therapeutics and provides a comprehensive review of the biology of asthma, deficiencies of current corticosteroid treatments, the mechanism of action of treatments, and new and emerging forms of treatment for asthma, including recent discoveries linking gut health to asthma.

Introduction

Asthma is a prevalent respiratory condition that affects millions worldwide. According to the National Library of Medicine, over 300 million people globally will have asthma in 2024 (Wong et al., 2020). According to the National Center for Health Statistics, in the United States, 27 million people were affected by asthma, and 4.5 million of them were children in 2022 (CDC, 2024). Asthma is one of the most common diseases in the United States, with 1 in 12 people affected by this condition (AAFA, 2024). In 2019, asthma caused 455,000 deaths worldwide and 3,542 in the United States (WHO, 2024). 1,000 asthma-related deaths occur every day (Global Asthma Network, 2022). Many of these deaths occur in lower-income countries, as access to a proper diagnosis and treatment is limited (Barne, 2023).

Asthma also has a notable economic impact. According to a CDC study conducted in 2018, medical expenses from asthma cost the U.S. economy over $80 billion annually (Inserro, 2023). In 2021, the market value of asthma treatment was $25 billion, and the market is expected to grow to over $30 billion by 2027 (Biospace, 2023). This growth is largely driven by ongoing advancements in asthma treatments, including inhalers, biologics, and other medications designed to manage asthma symptoms and prevent asthma attacks (Global Market Insight, 2024).

Despite advances in patient care for asthma, there are still many asthma-related deaths occurring each year. Corticosteroids are the main form of medication to treat asthma, but these medications such as Flovent, Qvar, and Asmanex can have adverse side effects that make it extremely hard for patients to

take medicine multiple times a day to treat their asthma. This paper will highlight the biology of asthma, deficiencies of current corticosteroid treatments, the mechanism of action of treatments, and new and emerging forms of treatment for asthma, including recent discoveries linking gut health and asthma.

Biology of Asthma

Asthmatic events can be triggered by a variety of factors, including allergens and respiratory infections. Common allergens that provoke asthma symptoms include pollen, dust mites, pet dander, and mold (Better Health Channel). Environmental irritants such as air pollution, cigarette smoke, and chemical fumes can also aggravate asthma (Better Health Channel). Additionally, respiratory infections, particularly infections like COVID-19, the common cold, or the flu, are significant triggers for asthma (AAFA). Physical activity or stress can also induce asthma symptoms in some individuals (Better Health Channel). Asthma is typically accompanied with symptoms such as coughing, shortness of breath, wheezing, and chest pain (AAFA). These symptoms are caused by the lining of the airways becoming swollen or inflamed, due to irritation from an allergen (Cameron, 2024).

Genetic factors play a key role in determining who has asthma, and how severe it is. Certain genes can make people more likely to develop asthma by affecting the immune system and how their airways respond to inflammation. Some of the key genes involved are ORMDL3, ADAM33, HLA-DQ (A1/B1), and Filaggrin (Shabir, 2022). All the genes listed are involved in either inflammation, immunity, or lung function (Shabir, 2022). For brevity, the two established genes, ADAM33 and ORMDL3 will be briefly discussed.

The ADAM33 gene contributes to asthma by causing changes in the structure and function of the airways. It affects the growth of fibroblasts, smooth muscles, and the deposition of matrix proteins, leading to thickening of the airway walls and making it harder to breathe.
Some forms of ADAM33 can also cause abnormal blood vessel growth in the airways (Mahesh, 2013).

The ORMDL3 gene, on the other hand, primarily influences immune system regulation and inflammation. It helps control sphingolipid metabolism, which is important for cell signaling. Disruption in this process can lead to increased inflammation in the airways. ORMDL3 is also involved in the unfolded protein response (UPR) within cells, which, when dysregulated, can also contribute to inflammation in the lungs. Elevated levels of ORMDL3 have been linked to increased production of pro-inflammatory cytokines, making the airways more sensitive to asthma symptoms (Gui et al., 2021).

Mutations or polymorphisms occurring in any of these genes hinder their normal function, leading to an unbalanced immune system, decreased lung function, or airway hyperresponsiveness (Shabir, 2022). These genes either contribute to early-onset asthma or cause susceptible adults to develop asthma later in life due to environmental factors such as smoking or pollen (Shabir, 2022).

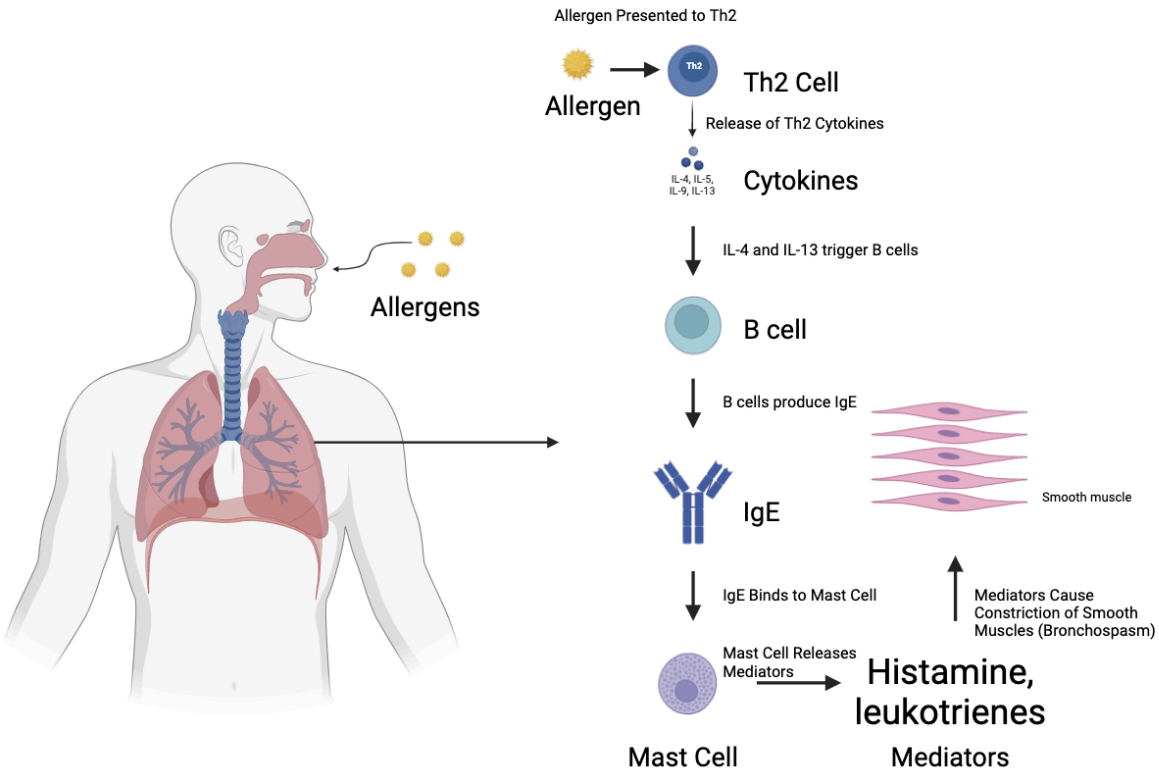

Figure 1. Signaling Events Leading to an Asthma Attack After Allergen Exposure. Inhaled allergens set up a chain of events that amplify inflammation, leading to bronchospasm and airway swelling.

On a molecular level, an asthma attack involves a series of reactions. When someone with asthma inhales an allergen, it is recognized by antigen-presenting cells in the airways (Figure 1) (Habib et al., 2022). These cells present antigens to Th2 (T-helper type 2), which release Th2 cytokines, specifically IL-5, IL-4, and IL-13 (Habib et al., 2022). IL-4 and IL-13 trigger B cells, which produce IgE (Immunoglobulin) and bind to the FcεRI of mast cells (Habib et al., 2022). When the same allergen is encountered, it binds to IgE, causing mast cells to release mediators such as leukotrienes or histamine (Habib et al., 2022). IL-5 on the other hand, enables eosinophil (a type of white blood cell) production and maturation, and directs the eosinophils from the bloodstream into the lungs (Habib et al., 2022). Once in the lungs, eosinophils, along with other immune cells like mast cells, release substances such as histamine and leukotrienes that cause bronchospasm, the inflammation and swelling of the airway walls (Habib et al., 2022).

Current Asthma Action Plans and Limitations

Asthma attacks can be life-threatening and typically require immediate intervention. An asthma action plan typically includes both bronchodilators and corticosteroids because they address different aspects of the disease and have complementary effects to manage symptoms and prevent asthma attacks. Corticosteroids help prevent inflammation and long-term damage, while bronchodilators provide immediate relief during asthma symptoms or attacks, ensuring optimal asthma control.

Bronchodilators such as albuterol or levalbuterol are the primary medications used for quick relief during an asthma attack. These bronchodilators work by targeting the beta-2 receptors on the muscle cells of the airways, causing these muscles to relax and subsequently dilate, making it easier to breathe. Bronchodilators are typically administered through inhalers or nebulizers, and provide relief of symptoms within minutes (NIH, 2020).

Corticosteroids, including inhaled corticosteroids such as Flovent, QVAR, and Asmanex, reduce inflammation in the airways which plays a key role in asthma by causing mucus production and airway constriction. Corticosteroids also provide long-term control for asthma by reducing airway inflammation and hyperresponsiveness, which helps prevent and mitigate asthma attacks. While Corticosteroids are effective in asthma management, their side-effects include but are not limited to heart palpitations, dizziness, chest pain, hives, and in rare cases, high blood pressure or vomiting (Mayo Clinic, 2024). Long-term use in children can also have adverse impact on growth. Corticosteroids primarily suppress inflammation and immune responses but do nothing to address the underlying specific mechanisms that trigger asthma. These confluence of factors highlight the need for alternative treatments that are more targeted in managing asthma.

Recent Biological Therapies

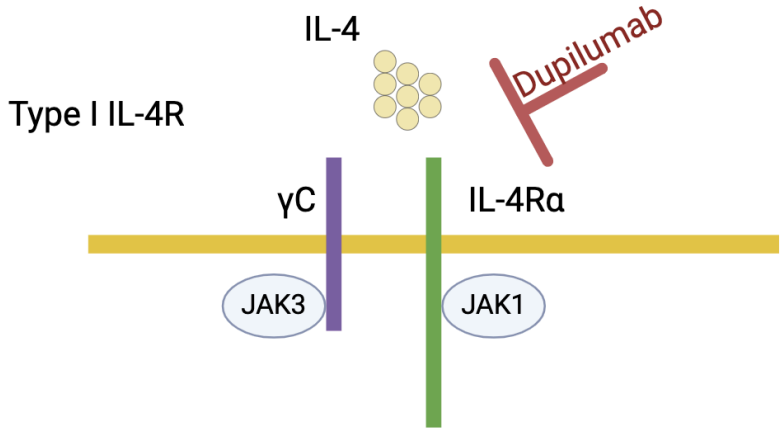

Figure 2. Mechanism of Action of Dupilumab. Dupilumab is a monoclonal antibody that inhibits cytokines to help reduce inflammation and improve asthma symptoms.

IL-4, IL-5, and IL-13 are key cytokines produced by Th2 cells that play significant roles in asthma. Dupilumab is a monoclonal antibody that inhibits both IL-4 and IL-13. It works by binding to the IL-4 receptor alpha (IL-4Rα), which is part of the receptor network for both IL-4 and IL-13. IL-4Rα is expressed on a variety of immune cells such as T cells, B cells, macrophages, natural killer cells and dendritic cells, all of which are involved in pro-inflammatory pathways such as those in asthmatic events. By preventing these cytokines from interacting with their receptors, Dupilumab inhibits them from triggering other cells that lead to inflammation and bronchospasm (Figure 2) (NIH, 2019). Dupilumab is given by injection under the skin once every two weeks in adults and children older than 12, and once every four weeks in children 6 months to 11 years old (National Eczema Association).

There are also currently three FDA approved IL-5 blockers on the market for asthma. They are Mepolizumab, Benralizumab, and Reslizumab (Mayo Clinic, 2020). Mepolizumab is specifically used to prevent common asthma symptoms, such as wheezing, difficulty breathing, tightening of the chest, and coughing. It is intended for those six years and older, and only if their asthma symptoms are not controlled with their current medications. This treatment is sold under the name Nucala, owned by the biopharma company GlaxoSmithKline. It is administered through injection once every four weeks. Benralizumab is also used to prevent asthma symptoms in those whose symptoms cannot be controlled by steroid medication. The first three doses of Benralizumab are given every four weeks, and then one dose every eight weeks. This medication is known as Fasenra, and is sold through AstraZeneca Pharmaceuticals. However, unlike the other two IL-5 blockers, Reslizumab is used specifically as an add-on treatment for severe eosinophilic asthma and is to be taken alongside oral steroid medications. It is not to be used for acute bronchospasm. Like Mepolizumab, this medication is given once every four

weeks through an IV infusion. Reslizumab is marketed under the name Cinqair, and was developed by Teva Pharmaceuticals. These IL-5 blockers work by binding to IL-5, which prevents it from interacting with its IL-5 receptor on the surface of eosinophils. By blocking IL-5, these treatments reduced the blood eosinophils count, leading to decreased inflammation and prevented asthma attacks (Zhao et al., 2010). While these treatments are well accepted, they can cause side effects such as headaches, injection site reactions, upper respiratory tract infections, and in less frequent cases hypersensitivity and fatigue (Dai et al., 2021). As such the treatments should be used with caution in certain patients.

New Gene Therapies

Gene therapy is a cutting-edge approach to treat asthma by targeting specific genes involved with the disease. One of the most promising tools for gene therapy is the CRISPR-Cas9 system, which allows for precise gene editing. The CRISPR-Cas9 system has two main components: guide RNAs (gRNAs) and the Cas9 endonuclease. gRNAs are small pieces of genetic material designed to bind a specific gene within a cell. Once they identify the gene of interest, gRNAs direct Cas9 to the precise region of DNA that needs to be deleted or edited. When Cas9 cuts the gene specified by the gRNA, repair mechanisms are used to fix the break in the DNA. One method allows scientists to create gene knockouts that remove or inactivate a specific gene (Sampath, 2018).

Researchers at the Sean N. Parker Center for Allergy and Asthma Research at Stanford University are using CRISPR-Cas9 gene-editing technology to screen 800 kinases in the human body. This collaboration with Integrated DNA Technologies (IDT) aims to identify genes associated with asthma and allergies. By creating gene knockouts, scientists can study the role of specific genes in allergic reactions and asthma attacks, allowing them to better understand gene functions. This research may lead to discovering new drug targets and therapeutic treatments for asthma, potentially improving asthma symptoms (Sampath, 2018).

This technology can be extremely useful for asthma, as researchers can use CRISPR-Cas9 as a way to create gene knockouts in Th2-asthma related cells that were discussed earlier. Th2 cells are known to secrete inflammatory molecules (cytokines) that activate B cells to secrete IgE, a key substance involved in allergic diseases. When IgE binds to mast cells, an individual can develop sensitivity to that allergen. Upon exposure to allergens, mast cells immediately begin to secrete molecules such as histamine, which causes the common symptoms of asthma. Researchers have recently identified key genes associated with Th2 cells that may be involved in asthma. Through creating gene knockout cells through CRISPR-Cas9, it is possible to knockout disease-related Th2 cells, rendering them inactive and unable to produce substances that lead to asthma, such as IL-4, IL-5, and IL-13 (Sampath, 2018). While CRISPR is highly precise, it is not perfect and can lead to unintended gene editing that could cause harmful mutations. CRISPR may also trigger an immune response, potentially leading to inflammation or allergic reactions. More research, safety assessments, and clinical trials are required to mitigate these risks.

Emerging Gut-Lung Axis

The gut-lung axis is an emerging area of research that explores how a person's gut health can impact lung health. This connection suggests that the state of our gut microbiome may influence conditions like asthma.

The gut microbiome includes fourteen core bacterial groups and 150 bacterial species, while the lung microbiome only has seven bacterial groups. One major difference between the two is that the gut microbiome has higher alpha diversity, meaning a wider variety of bacterial species are present in larger quantities. The dominant microbial phyla in the gut are Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia, with Firmicutes and Bacteroidetes representing 90% of the gut microbiota. These include genera like Lactobacillus in Firmicutes and Bacteroides and Prevotella in Bacteroidetes (Bousquet et al., 2019). In contrast, the lung microbiome has fewer dominant phyla, with Firmicutes and Bacteroidetes also present, but fewer genera overall, such as Prevotella, Porphyromonas, and Streptococcus (Beasley et al., 2022).

The diversity and abundance of species in the gut microbiome are important because they can influence immune function beyond the gut. The gut microbiome produces molecules like short-chain fatty acids (SCFAs), that can mobilize host immune cells that travel through the bloodstream to the lungs. These circulating cells can affect lung immunity and potentially change the composition of the lung microbiome.

This interaction is particularly relevant for asthma.The gut microbiome affects asthma severity by influencing inflammation and immune responses. When the gut microbiome is out of balance, also known as dysbiosis, it can lead to lower levels of beneficial bacteria that produce short-chain fatty acids (SCFAs) like butyrate, which help reduce inflammation and maintain a healthy gut barrier. Although regular levels of SCFA protect against asthma symptoms to a certain extent, lower SCFA levels can worsen asthma by increasing inflammation and making the airway more susceptible to allergens, as the ability to activate Th2 cells is impaired (Wenzel et al., 2022). A study by Lancet Respiratory Medicine has shown that children with a gut microbiome capable of producing more SCFAs have decreased rates of asthma later in life (Morris et al., 2020). However, children with a gut microbiome that produces less SCFAs have an increased risk of asthma development. SCFAs can reduce the number of IL-4 producing CD4+ T cells, which are crucial to the Th2 immune response that leads to asthma. This reduction in IL-4 production helps lessen the severity of asthma symptoms by reducing the body's allergic responses (Alvarez et al., 2017).

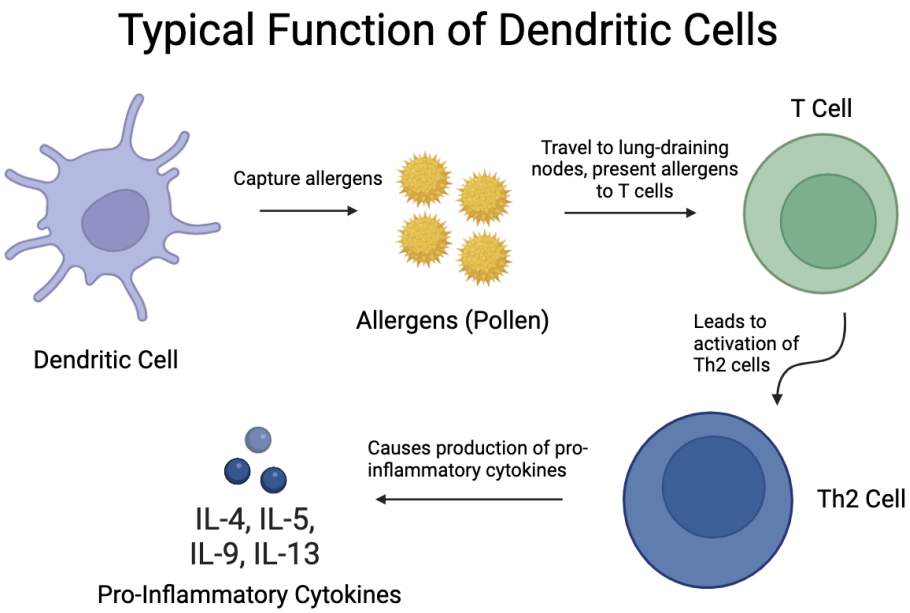

Figure 3. Typical Function of Dendritic Cells (DCs). DCs initiate and regulate immune responses by capturing allergens, transporting them to lung-draining nodes, and presenting them to T cells. This activates Th2 cells, leading to IL-4 production and an inflammatory response in the lungs, triggering asthma symptoms.

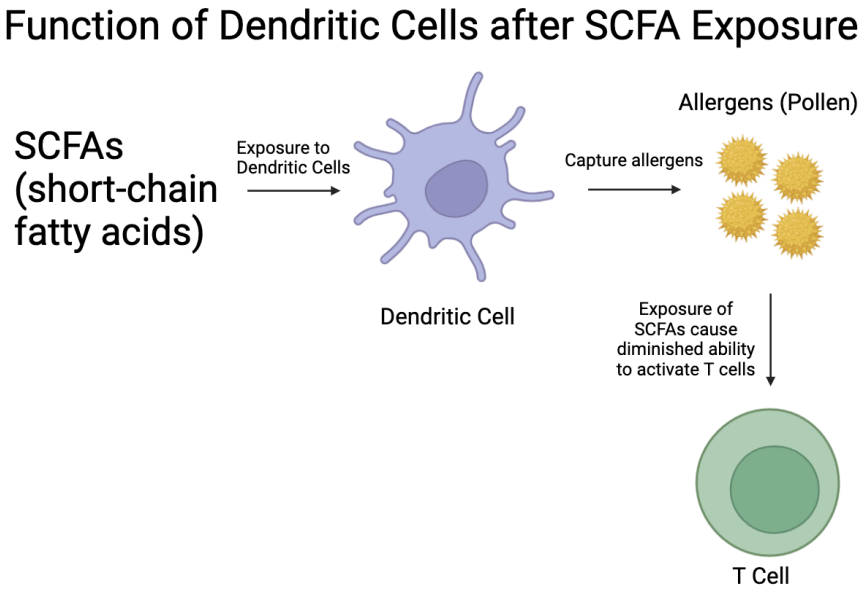

Figure 4. Function of Dendritic Cells After SCFA Exposure. SCFAs reduce dendritic cells' (DCs) ability to activate T cells and transport allergens to lung-draining nodes. This weakens the immune response that triggers asthma by reducing Th2 activation and cytokine production, ultimately decreasing lung inflammation.

SCFAs also have an impact on dendritic cells (DCs). When DCs are exposed to SCFAs, their ability to activate T cells and transport inhaled allergens to lung-draining nodes is diminished. This is important because DCs play a crucial role in initiating immune responses, particularly for asthma. Typically, DCs capture allergens that enter the lungs and then travel to lung-draining nodes, where they present these allergens to T cells. This process triggers an inflammatory immune response, which includes the activation of Th2 cells, leading to the production of pro-inflammatory cytokines such as IL-4. These cytokines promote the inflammatory immune response in the lungs that is presented as an asthmatic event (Figure 3). By reducing the DCs' capability to activate T cells and transport allergens, SCFAs essentially slow down or weaken this entire chain of events. This impact of SFCAs means that the immune system is less likely to overreact to allergens, therefore reducing the severity of asthma inflammation in the lungs. This reduction shows how SCFAs produced in the gut affect asthmatic events via the immune system (Figure 4) (Gibson et al., 2017).

Additionally, SCFAs modulate gene expression, specifically through the transcription factor FOXP3. By inhibiting histone deacetylation, SCFAs allow for the increased expression of FOXP3. FOXP3 is essential for the development and function of regulatory T cells (Tregs). Tregs help prevent the immune system from overreacting to harmless substances like allergens. This action is particularly important when considering asthma, where an overactive immune response can lead to inflammation and bronchospasms typical of asthma (Tariq et al., 2022).

The anti-inflammatory effects of SCFAs also reduce levels of circulating IgE, which is an antibody type associated with allergic responses. Studies have shown that dietary supplementation with SCFAs can decrease IgE levels, leading to a reduced risk of airway inflammation (Alvarez et al., 2017). Likewise, the modulation of the gut microbiome by SCFAs has been linked to asthma outcomes. For example, children with higher levels of butyrate and propionate in their feces at 1 year old have been found to have lower rates of atopic sensitization and are less likely to develop asthma later in childhood compared to those 3-6 years in age (Koskela et al., 2022).

Lastly, SCFAs help increase the number of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs), which are regulators in airway inflammation. PMN-MDSCs work together with Tregs to keep the immune system from overreacting and causing too much inflammation. In a small animal study investigating myeloid-derived suppressor cells (MDSCs) and Treg cells, it was found that when mice treated with SCFA-containing drinking water, there was amelioration of allergic airway inflammation. The mice receiving the SCFA-containing water developed less severe asthma than the mice who didn’t receive it. The authors reported that this protective effect was due to the cooperation of PMN-MDSC and Treg induction (Chen et al., 2023).

Conclusion

Asthma continues to be a major global health issue, affecting millions of people and causing significant health and economic challenges. Current treatments such as inhaled corticosteroids are the standard, and these therapies focus on reducing inflammation and quickly relieving bronchospasms. Inhaled corticosteroids, such as Flovent, Qvar, and Asmanex, are typically prescribed to control chronic asthma, while bronchodilators like albuterol provide rapid relief during acute attacks. However, many of these

treatments come with side effects and sometimes may not even calm asthma symptoms, especially for those with severe forms of asthma.

Emerging treatments such as Dupilumab, Mepolizumab, Benralizumab, and Reslizumab, function by blocking IL-4, IL-5, and IL-13, pro-inflammatory cytokines that exacerbate asthma symptoms. Also, gene-editing techniques like CRISPR-Cas9, show promise in providing effective care by knocking out disease-related Th2 cells, causing them to be unable to produce these pro-inflammatory cytokines. These advancements could help manage asthma better by addressing the underlying immune responses that lead to inflammation and breathing difficulties, and could potentially reduce the need for daily medications.

In addition to advancements in medication, the relationship between the gut microbiomes and lungs is a newer field in asthma research. The gut-lung axis suggests that maintaining a healthy gut microbiome, particularly through the production of short-chain fatty acids, can have protective effects against asthma by modulating the immune response and reducing inflammation. Ongoing research and advancement into the role of SCFAs, along with treatments such as gene therapy, could transform asthma care in the coming years, improving outcomes for patients and possibly reducing the global issue of asthma.

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