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REVIEW ARTICLE

Effects of Epigenetics on miRNAs and the Function of T Cells in Allergic Diseases

Heidi Chen

Ursuline Academy of Dallas, 4900 Walnut Hill Ln, Dallas, TX 75229, USA; heidipachen08@gmail.com

ABSTRACT: Especially with their inflammatory responses, immune T cells play a large role in the development and severity of allergic diseases. In recent studies, epigenetic modifications, specifically types that affect microRNAs (miRNAs), were shown to have the ability to significantly influence gene expression regulation in various T-cell subsets. Many epigenetic modification mechanisms, such as DNA methylation and histone acetylation, have been proven to successfully modify miRNAs along with T cell differentiation in allergic diseases. A secondary analysis was conducted using databases of ScienceDirect, Google Scholar, and PubMed to gather data. This article will explore the effects of epigenetic modifications that target miRNAs on T-cell function in allergic diseases such as atopic dermatitis, asthma, and chronic urticaria. Although these epigenetic methods can help noninflammatory regulatory T cells suppress proinflammatory T cells, the risks of these changes include mutations that worsen the allergic reaction. Because of this, researching the effects of epigenetics on T cells is crucial as it can lead to a deeper understanding of allergic inflammation and specific miRNAs affected by immune dysregulation, potentially aiding in future developments of more effective and longer-lasting treatments.

KEYWORDS: Cellular and Molecular Biology, Genetics, Epigenetics, Allergic Diseases, T cells.

Introduction

Allergies are becoming an increasingly widespread major health concern, with skin inflammation in allergic skin disorders creating significant risks to patients' health. One significant contributing factor to the adaptive immune system is T cells, specifically, regulatory T cells (Tregs), a subset of CD4+ T cells. These Tregs are responsible for maintaining immune tolerance as they suppress excessive allergic inflammatory reactions.[1] Another type of distinct immune cells, mast cells are involved with provoking immediate allergic reactions, releasing histamines and cytokines when they bind to allergen-specific IgE.[2] Other innate immune cells that also advance the pathogenesis of allergic diseases include eosinophils, basophils, and dendritic cells.

Micro-RNAs (miRNA) are a large subgroup of non-coding RNA that usually suppress gene expression. Additionally, they have been found to have the ability to influence regulatory systems involved in the inflammation of some skin diseases.[3,4] There are several major variational methods for epigenetic modifications, with the most prevalent being DNA methylation. Epigenetic processes can both directly and indirectly modify gene expression, such as blocking TFs (transcription factors) and preventing regulatory elements from receiving positive transcription signals;[5] helps sustain long-term gene expression in memory T cells, improving the enhanced effector response;[6] and regulate cytokine genes to affect the ability of CD4+ and CD8+ T cells to produce the necessary cytokines for immune responses.[6,7]

Epigenetic modifications have the ability to modify various miRNAs in allergic diseases to suppress immune responses. Although additional research still needs to be conducted, current evidence suggests that immunotherapeutic approaches targeting miRNAs in the immune system can be effective in stabilizing Tregs long-term for disease prevention and, along with many other potential outcomes of this treatment, in reducing skin barrier damage by inhibiting Th2 inflammatory cytokine.[7,8]

In allergic diseases, there is a clear difference in the number of regulatory T cells, the level of miRNAs, the balance of Th1 and Th2 cells, and the number of allergen-specific memory T cells between patients with and without the disorder. Because the majority of the outcomes of miRNA modulation are heavily dependent on individual circumstances and factors, including the miRNAs involved, the severity of allergic disease, and the cell types affected, there are several approaches to achieve a lowered severity of an allergic reaction. While a decrease in some miRNAs could benefit the situation, an increase in different miRNAs within the disorder could lead to the same overall effect.[4] Recent studies have primarily focused on the identification of Treg cell development and potential molecular treatments and suppression techniques. The continued discussion of Treg involvement will be important for developing treatments that target Tregs to alter its suppressive and restorative ability allowing it to better regulate allergic and autoimmune diseases.[7] Additionally, there have been studies conducted that identified several miRNAs not only as biomarkers but also as possible therapeutic agents for chronic skin disorders.[8] However, there are still many unexplored factors that need to be taken into consideration while developing treatments and drugs for clinical use. This article will explore the effects of epigenetic modifications that target miRNAs on T cell function in some of the most common allergic diseases,

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specifically atopic dermatitis, asthma, as well as chronic urticaria.

Discussion

DNA methylation and the function of T cells:

DNA methylation, being one of the primary methods of epigenetic editing, is capable of mediating the effects and risks within the development and progression of allergic diseases. This process can largely alter T cell function, and consequently, the immune system's response to external stimuli.[9] In addition to its role as a gene expression regulator, DNA methylation and imbalanced epigenetic gene regulations in general have been linked to several human disorders, especially observable in children. The epigenetic method of DNA methylation can be defined as a heritable epigenetic marking of a covalent transfer of a methyl group to the base cytosine ring in DNA-by-DNA methyltransferases (DNMTs). Different types of DNMTs, such as DNMT3a and DNMT1, each have a role in the methylation process that can determine the success of the epigenetic modification. Although able to work in cytosines anywhere within the genome, a large majority of DNA methylation takes place in CpG dinucleotides specifically.[10] Another product of DNA methylation is restricting gene promoters from transcription factors (TFs), which directly prevents those TFs from binding.[11]

T lymphocytes (T cells) are a subset of white blood cells responsible for immune responses and the surfacing of allergic symptoms. As T cell receptors (TCRs) recognize cognate antigens presented by major histocompatibility complex molecules (MHC) on antigen-presenting cells (APCs), T cells will undergo activation and clonal expansion to regulate immune responses.[12] These T cells can then be further categorized according to their specific function after having completed the process of T cell differentiation. This differentiation occurs after positive and negative thymic selection when naive cells are exposed to antigens of MHC molecules. During this, naive T cells are epigenetically reprogrammed and develop into either CD4+ T effector cells or CD8+ cytotoxic T cells, both of which are produced by the thymus. The two divisions of T cells are discerned based on their surface proteins and transcriptional programs throughout their development.[13] After their maturation in the thymus, naive antigen-specific CD4+ T cells are then distributed to peripheral tissues where their essential function is to support the immune system. When they interact with foreign antigens or APCs, they differentiate into various subsets of helper T cells and regulatory T cells depending on their surrounding environment and the polarizing cytokines involved.[14] The cells and their respective cytokines are connected to the development of several immunological illnesses including allergic diseases.

In allergic diseases such as asthma, urticaria, and atopic dermatitis, there is often a skewing of T helper 2 (Th2) cells that affects the immune pathway related to differentiation. Particularly with eosinophilic inflammation – which is related to eosinophils, white blood cells that can accumulate in patients' airways – some studies have theorized that the development of inflammation in allergic airway diseases can be associated with a dominant differentiation of Th2 cells, which produce IL-4, IL-5, IL-12, and IL-13 cytokines (Figure 1).[15] Given this hypothesis that Th2 cells and their cytokines have a strong influence on asthma pathophysiology, inducing a Th1 response was thought to be a promising solution. Surprisingly, Th1 cells and their IFN-γ cytokine were found to have potentially pro-inflammatory effects in the lung, contrary to the original theory. Unfortunately, due to a lack of consistent testing, results of studies on Th1 cells and their cytokines remain conflicting, with some results demonstrating dampening capabilities, while others find them to have pro-inflammatory effects on allergic diseases.[15]

Despite its known contributions, Th1 and Th2 are not the only cells that contribute to allergic reaction severity and sensitization towards treatments.[16]

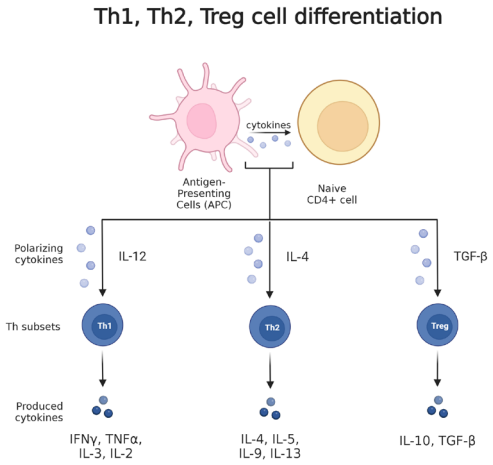

Figure 1: This figure illustrates the process of naive CD4+ T cell differentiation into Th1, Th2, and Treg Cells based on the cytokines involved. The polarizing cytokines are the determining factor for which subset the cell becomes: IL-12 induces CD4+ T cells into Th1 cells, the cytokine IL-4 promotes the differentiation into Th2, and TGF-beta cytokines into Treg cells. This diagram was created using BioRender.

Another subset of CD4+ T cells that also has the ability to inhibit the immune system is known as regulatory T cells (Tregs). By maintaining peripheral tolerance and immunological homeostasis, Tregs can contribute to the prevention of allergy disorders altogether.[17] There are two main subtypes of regulatory T cells based on where they develop: ones developed in peripheral tissues are known as pTregs, while ones in the thymus are called tTregs. Through cell-to-cell interactions and moderating inhibitory cytokines, regulatory T cells can prevent immunological responses. However, to maintain and manage Treg stability and function, epigenetic regulation mechanisms, including DNA methylation and histone modifications, are essential.[7] Although Tregs are important in allergic illnesses, it is unknown how and why a patients' tolerance can fail, but there are multiple treatments currently in trials for an eventual clinical application (Table 1).

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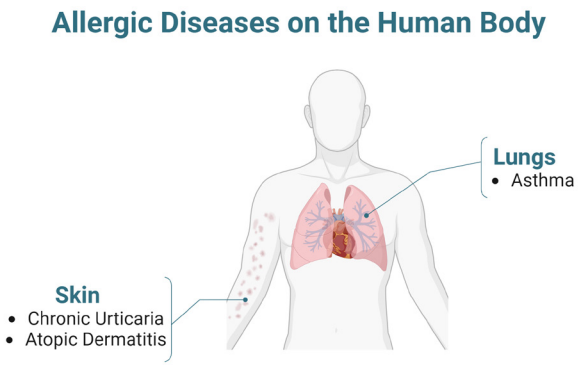

Figure 2: This figure illustrates where individual allergic diseases affect the human body. Both Chronic Urticaria and Atopic Dermatitis affect the skin, while asthma affects the lungs. This figure was made using BioRender.

Epigenetics on T cells in asthma:

By targeting Treg cells, there is potential for epigenetics to mediate the impact environmental factors have on the progression of allergic disorders like asthma.[5] Asthma is a clinically heterogeneous chronic airway inflammatory disease characterized by symptoms of wheezing, shortness of breath, chest tightness, and coughing (Figure 2).[7,18] miRNAs are one of the factors of the regulatory mechanisms that are involved with allergic diseases like asthma.[19]

For example, miR-155 and miR-221 have both been associated with Th2 responses along with several cellular elements of allergic responses including eosinophils, macrophages, and mast cells in asthma and allergic rhinitis. MiR-221 specifically targets genes involved in immune response and an increase in them would lead to an exacerbation of asthma symptoms including airway hyperresponsiveness and inflammation.[20] MiR-155 targets and suppresses genes that negatively regulate immune responses. This miRNA is often upregulated in airway tissues of asthma patients, and it has the potential to be used as a target therapeutic strategy in terms of reducing Th2-drive inflammation.

Allergic asthma disease is considered a T helper (Th) cell-mediated disease that has been thought to be brought on by a combination of environmental factors and some genetic predispositions.[9] Specifically, when there is a defective production of Th1 or T-bet cells, allergic asthma is actively present. Additional research examined genome-wide DNA methylation and gene expression patterns in both IL-13-treated and untreated airway epithelial cells. Produced by Th2 cells, the cytokine IL-13 is considered one of the main upregulated mediators in asthma. The findings demonstrated that IL-13 exposure can cause changes in DNA methylation in asthmatic airway cells, as well as contribute to asthma phenotypes.[19] DNA methylation methods in Th1 and Th2-produced cytokine genes were also explored, concluding that T cells can contribute to the development and eventual sensitization of asthma. After21 Results indicate that nasal DNA methylation has the potential to be a biomarker for IgE sensitization which suggests the individual is at a high risk of allergic respiratory disease.[22] Not only is this beneficial for asthma, but similar marks were also discovered in patients with rhinitis, showing the versatility of the efficacy of DNA methylation in various allergic diseases.

Furthermore, Th2 cytokine inhibition has been suggested as the most promising approach and anti-IL-5 treatment is the most successful for reducing asthma exacerbations.[23] As a response to allergen exposure, Tregs can inhibit pathways of allergic sensitization and IgE production. Patients with severe asthma tend to display comparatively lower levels of FOXP3+ Tregs and a reduced amount of circulating Tregs. Similarly, there was an increased frequency of CRTH2+ Tregs in patients with acute asthma. Overall, asthmatic patients inhabit a lower number of Treg cells, demonstrating a decreased lower functionality and a Th2 preference behavior.[7] With Tregs and Th cells playing such a large role in asthma regulation, modifications of miRNAs that impact those cells can, as a result, mediate the impact cytokines produced by those cells have on the pathogenesis of the disease.

MiRNA and Treg Function in AD:

Caused by genetic, environmental, and immunological factors, atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder that affects a significant number of adults and children (Figure 3). AD disorder has symptoms of severe skin dryness, itching, and rashes. These allergic inflammatory reactions can be brought on by a combination of the environment and the patients' genetics. Th2 cell hyperactivation in AD can cause persistent inflammation and a weakening of skin barrier functions. Other subgroups of T helper cell responses such as with Th22 and Th17 can also contribute to AD development through skin and blood infiltration.

Atopic dermatitis is also associated with Tregs, cells that typically aid in the regulation of immune responses by suppressing other immune cells. Treg dysfunctions have been connected to AD due to their observed frequency in other similar genetic illnesses that share skin abnormalities with AD such as immunodeficiency and Wiskott-Aldrich syndrome.7 In AD specifically, Tregs can have a reduced suppressive function. This reduced function could then lead to an inability to control Th2 cell activity and result in chronic inflammation and a worsening of symptoms. Tregs are also involved in maintaining the skin barrier. Their dysfunction in patients with AD can intensify skin barrier defects, allowing allergens to penetrate the skin which would trigger further immune responses (Figure 3).[8] Able to infiltrate the skin and regulate immune responses, Tregs are increasingly explored for their relevance in various genetic and allergic disorders. With a recent study showing a noticeable decline in the severity of AD after AIT treatment and vitamin D supplements, there is evidence to support that both methods contributed to either an increase in Tregs or an enhanced function in existing cells.[7]

MiRNAs have been known to be involved in multiple immunologic and inflammatory disorders. Due to its strong overexpression in several immune cell types such as mast cells, fibroblasts, and lymphocytes cells involved in the pathophysiology of chronic skin inflammation, the miRNA miR-155 has commonly been linked to inflammation in skin disorders. It was suggested to potentially have a regulatory effect on T helper cells based on its upregulation in multiple cell lineages.

Individuals with AD were shown to have varied expressions of miR-155 in their skin and peripheral blood vessels.[4] The research concluded that patients with AD had a higher expression of miR-155 in both peripheral CD4 T cells and various skin specimens and that there was a relatively positive correlation between the number of CD4 T cells present in a patient and the severity of AD disease.[24]

As studies have continued to investigate DNA methylation changes in AD, researchers demonstrated a strong correlation between CpG methylation changes in keratinocytes and innate immune cells and altered gene expressions causing skin barrier dysfunction and inflammation. Especially in immune cells, hypomethylation of the Il-13 cytokine was connected to an increased Il-13 expression, demonstrating epigenetic modulation of Th2 cell inflammation.[25] These results emphasize the role of DNA methylation in immune responses of Atopic Dermatitis, further implying its potential as a therapeutic target.

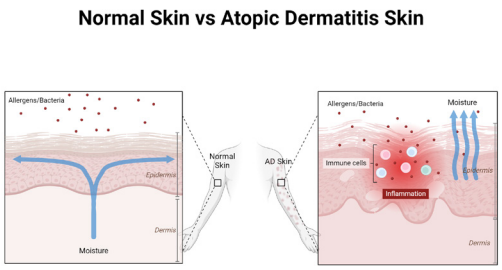

Figure 3: This comparison between normal skin and AD skin demonstrates a damaged skin barrier. On the left with the normal skin, a healthy barrier is intact which allows the skin to retain moisture. This prevents allergens and bacteria from entering the skin. On the other hand, atopic dermatitis skin on the right has a disrupted barrier function. This allows allergens and bacteria to penetrate the skin. The presence of immune cells reflects an active immune response which leads to inflammation from immune cell activation in response to the invading allergens/bacteria. The figure was made using BioRender.

miRNAs in Chronic Spontaneous Urticaria:

Chronic spontaneous urticaria is an allergic disease that can be defined as the spontaneous presence of itchy hives for six weeks or longer (Figure 2).[8] Despite its prevalence, the pathophysiology of chronic spontaneous urticaria (CSU) is largely unknown. However, two main pathogenetic mechanisms are thought to be responsible for the disease. The first of which involves the presence of autoantibodies to immunoglobulin E (IgE) on mast cells and basophils.[26] The autoantibodies can cause immune cells to release histamine and other inflammatory mediators, contributing to the development of hives on the skin. The second mechanism is related to the dysregulation of regulatory and immune signaling pathways within those cells, which results in an inflammatory response.[8,27]

Epigenetic research on skin conditions such as urticaria has contributed greatly to existing knowledge of the processes of gene regulation. Research has determined that there are five significantly upregulated miRNAs in CSU: miR-2355-3p, miR-4264, miR-2355-5p, miR-29c-5p, and miR-361-3p27. As a result, it can be implied that genes targeted by these miRNAs could be severely inhibited and can be used as biomarkers for urticaria disease.[3]

Overall, epigenetic processes like DNA methylation can regulate gene expression and immune responses in allergic diseases. These mechanisms can affect T cells, specifically T helper 1 (Th1), T helper 2 (Th2), and regulatory T cells (Tregs). As allergies are becoming increasingly prevalent and with inflammation causing increased health risks, there is a need for further advancements in treatment techniques. Currently, research has determined miRNAs as a reliable target to influence immune cell responses and reduce the severity of allergic diseases.[28]

In addition to miRNAs regulating immune cell functions, some genome-wide DNA methylation studies have been implicated in immune regulation through differentially methylated genes (DMGs). The study also identified several DMGs regulating the pathophysiology of CSU, which were heavily linked to immune pathways including cytokine signaling, mast cell activation, and inflammatory mediator regulation.[29] Thus, the studies concluded that epigenetic modifications, such as DNA methylation, are also suggested to be connected to the immunopathogenesis of CSU.

Despite the demand, further research and trials are necessary to better understand the complexities of epigenetic processes before an application of treatments for clinical approval. Some of the current miRNA-based treatments and therapies in trials are listed in Table 1.

Table 4: This table lists some of the current miRNA-based treatments and therapies directed at T-cell function in allergic disorders. Although there is constant progress being made toward miRNA-based therapeutics with some reaching clinical development, there are no therapeutics that have reached phase III human clinical trials or been approved by the FDA.[30] This figure was made using BioRender.

Altered miRNA	Treatment/ Trial	Function	Disorder	Status
miR-155	Anti-miR-155 Antagomirs	Regulate T-cell activation, Influence inflammatory responses	Atopic Dermatitis, asthma	Preclinical, early trials
miR-155	Toll-like Receptor 3 (TLR3) Agonist	Regulates inflammation and T cell responses	Atopic Dermatitis, asthma	Early-phase research
miR-21	MRX-21	Reduce inflammation and fibrosis	Atopic Dermatitis, asthma	Early clinical trials
miR-146a	miR-146a Mimics and Inhibitors	Regulate inflammatory responses and immune homeostasis	Chronic urticaria, asthma	Investigation, preclinical
miR-203	miR-203 Antagomirs	Reduce inflammation, regulate skin response	Atopic dermatitis, chronic urticaria	Preclinical
miR-34a	miR-34a Inhibitors	Modulate T cell differentiation, regulate inflammatory responses	Asthma, Allergic Rhinitis	Preclinical

■ Conclusion

Through an exploration of epigenetic processes, specifically DNA methylation and miRNA regulation, there is potential for its use in allergic illnesses such as chronic urticaria, atopic dermatitis (AD), and allergic asthma that can greatly contribute towards their understanding and development of treatments. As allergies become more prevalent in the world, there is an increasing risk of such diseases creating greater health risks due to the inflammation caused by their allergic reactions. From the research conducted, epigenetics of miRNAs has demonstrated potential for stabilizing noninflammatory regulatory T cells (Tregs) to reduce inflammation and, eventually,

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prevent the severity of allergic disease reactions from surfacing at all. Some studies recognize Allergen Immunotherapy (AIT) treatment to have the highest potential of fully suppressing allergic diseases as results have demonstrated a sustained healthy immune response to allergens. Because of miRNAs' involvement in regulating gene expression and inflammatory pathways, there is a higher likelihood of success if they are used for diagnostic purposes and treatments. Currently, the role of miRNAs in allergic diseases suggests that targeting and upregulating certain miRNAs could potentially have overall benefits. However, as a result of the complex process of miRNA modulation, there are many challenges presented for the further development of disease-specific treatments in addition to the opportunities for growth. This review discusses the effects of epigenetics, specifically DNA methylation, on allergic diseases as well as the various roles T cells can play in regulating their development. Some root causes for severe allergic reactions and the many areas for future development of treatments for specific allergic disorders were also identified.

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Author

Heidi is currently a junior in high school with a passion for biology, more specifically, immunology. She aspires to become a medical professional in allergy and immunology.

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