

Advances Of Allergen-Specific Th2 Cells in Atopic Diseases

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Abstract. Atopic diseases, such as atopic dermatitis (eczema), food allergies, allergic asthma, and atopic rhinitis (hay fever), involve our immune system overreacting to normally harmless substances. This can lead to chronic inflammation and various symptoms. In recent years, atopic diseases have become more prevalent around the world, affecting millions of adults and children (Thomsen, 2015). A particular type of immune cell, called allergen-specific Th2 cells, is known to play a vital role in the development of these conditions. This literature review aims to provide an overview of the current understanding on the role of allergen-specific Th2 cells in the pathogenesis of atopic dermatitis, peanut allergy, allergic asthma, and atopic rhinitis, with an emphasis on the biomarkers associated with their activation, recruitment, and effector functions. We will explore the molecular signatures of allergen-specific Th2 cells, their interaction with other cells and proteins, as well as their potential as therapeutic targets for atopic diseases.

Keywords: Allergen-specific Th2 cells, atopic dermatitis, peanut allergy, allergic asthma, atopic rhinitis.

1. Introduction

The term “atopy” was first introduced in 1923 by two American allergists as realizing the development of familial pattern of a certain disease either due to sharing genetics or similar exposed environments [1]. Atopic disease is nowadays understood as the genetic tendency to develop allergic symptoms in response to common environmental allergens. It often develops as an atopic march starting with the development of atopic dermatitis (AD) and food allergy (FA) during childhood followed by asthma and atopic rhinitis (AR). The frequency of these disorders has increased over the past few decades, resulting in a significant societal impact. In some countries, the incidence of AD in children is as high as 20% and continues to grow [2]. The quality of life for patients can be significantly impacted by having allergic reactions to substances that are otherwise non-harmful. Moreover, evidence has shown that patients with severe atopic disease have a 62% higher mortality rate compared to their counterparts [3]. Consequently, there is an urgent need to understand the pathogenic mechanisms of atopic diseases and identify possible therapeutic solutions.

Atopic disease is triggered by heightened immune responses to common allergens, which can be contacted, inhaled, or ingested. There are many factors that contribute to the pathogenesis of atopic diseases, including genetics and environmental influences. It is currently known that atopic disease is a type of type 2 inflammation triggered by allergen-specific Th2 cells -- thereafter abbreviated as asTh2 cells. Type 2 inflammation is an inflammatory process driven by a group of CD4⁺ T cells called Th2 cells. Upon exposure to allergens, Th2 immune response is activated by antigen presenting cells (APC), represented by dendritic cells. During the inflammatory reaction, activated T cells proliferate into allergen-specific Th2 cells to release interleukin-4 (IL-4), IL-5, IL-9, and IL-13. Specifically, IL-4 secreted by asTh2 cells sustains the lineage and attract additional T helper cells to the site. IL-13 then expresses CD40 ligand (CD40L), which, together with IL-4, promotes isotype switching in B lymphocytes towards immunoglobulin (IgE) production [4].

In 1992, Robinson et al. identified a specific subgroup of CD4⁺ T cells in patients with atopic asthma that responded to grass-pollen allergens, unlike in non-atopic patients. This subgroup of Th2 cells was characterized as asTh2 cells, which produce relatively high levels of IL-4, IL-5, IL-10 and IL-13. These cytokines are responsible for the activation of allergen-specific IgE [5]. Herein, we reviewed the biomarkers and biological properties of asTh2 cells in various atopic diseases to deepen our understanding of the underlying mechanisms that contribute to the development of atopic diseases.

2. Atopic Dermatitis

Atopic dermatitis (AD) is a widely prevalent type-2 inflammatory skin disease, affecting 3–7% the world population [6], with its rising prevalence in recent years. This persistent and recurrently inflaming skin disorder is characterized by symptoms such as eczema, intense itching, and ongoing inflammation.

Allergens such as peanuts, milk, and eggs have been identified as the common trigger in AD patients. These allergens are believed to trigger immune responses by activating asTh2 cells, which play a central role in AD pathogenesis. In 2002, Iwasaki et al. [7] discovered the prostaglandin D2 receptor CRTH2, which is uniquely expressed by asTh2 cells. Prostaglandin D2 (PGD2) is a lipid mediator that plays an important role in inflammation and allergy. It exerts its effects by binding to the CRTH2 receptor which is uniquely expressed in asTh2 cells. Activation of CRTH2 by PGD2 stimulates Th2 cell migration to sites of inflammation and promotes the release of cytokines IL-4, IL-5, and IL-13 that exacerbate the inflammatory responses, such as skin inflammation, itchiness, and barrier dysfunction.

In 2017, Mitson-Salazar and Prussin[8] identified a unique subpopulation of proinflammatory human Th2 cells known as IL-51 pathogenic effector Th2 (peTh2) cells that drive allergic eosinophilic inflammation in AD. These peTh2 cells, which exhibited a persistently stable IL-5+ phenotype, were found to be positive for hPGDS and expressed high levels of CD161. In 2021, Bangert et al. [9] further revealed that a specific subset of allergen-specific Th2 cells involved in the development of AD, known as proallergic Th2 (Th2A) cells, displayed high levels of IL-13.

Further supporting the role of asTh2 cells in AD, a 2022 study by McCluskey et al.[10] used bulk and single-cell RNA sequencing in an AD model to identify GATA3, a transcription factor critical for Th2 cell differentiation and function, as an efficient marker with high expression in asTh2 cells. Jiang and Sun subsequently suggested that GATA3 expression in asTh2 cells could be inhibited by sulfuretin, a natural anti-inflammatory compound. By suppressing GATA3 expression, sulfuretin could potentially reduce the production of Th2 cytokines including IL-4, IL-5, and IL-13, associated with inflammation and AD symptoms. In conclusion, hPGDS, CD161, IL-13, and GATA3 expression are all crucial markers associated with Th2 cell responses, emphasizing the pivotal role of asTh2 cells in AD pathogenesis.

In addition to these biomarkers, recent research has shed light on the influence of galectins, a family of carbohydrate-binding proteins, in mediating asTh2 cell responses on the pathogenesis of AD. Moar and Tandon [11] discovered that asTh2 cells are regulated by Galectin-9 (Gal-9) in the AD model. Gal-9 is a β -galactoside binding lectin primarily secreted by endothelial cells and has been found to play a significant role in the modulation of inflammatory responses. Gal-9 exerts its effects on asTh2 cells through a molecular interaction with cell surface protein disulfide isomerase (PDI). Specifically, Gal-9 binds to PDI on asTh2 cells, enhancing the retention of PDI on the cell surface. This interaction facilitates increased cell migration through the extracellular matrix via β 3 integrins, leading to inflammatory responses upon exposure to potential allergens[12]. These findings suggest that Gal-9 may play a crucial role in promoting asTh2 cell migration and the subsequent initiation of allergic inflammation. Moreover, Liu et al.[13] demonstrated in their 2018 study that another member of the galectin family, Galectin-3 (Gal-3), is related to asTh2 immune responses in mice. Gal-3 has been implicated in various immune processes, including cell adhesion, cell activation, and cytokine secretion. Importantly, all study results found a strong correlation between Gal-3/Gal-9 levels and the levels of Th2-released cytokines such as IL-4 and IL-10, further highlighting the significance of galectins in the regulation of Th2 immune responses in AD.

The role of chemokines in AD pathogenesis has garnered significant attention, with accumulating evidence suggesting that eotaxins, a group of chemokines, are directly linked to asTh2 cell activation and function. A study conducted in 2018 assessed AD skin biomarkers in Chinese patients and found robust activation of eotaxins in AD lesions, including CCL17, CCL18, CCL22, and CCL26. Interestingly, CCL26 was identified as a specific marker that distinguishes AD from psoriasis in the Han Chinese population[14]. Further investigations into the role of CCL26 have revealed its precise

activation of the chemokine receptor CCR3 on Th2 cells. Tian et al noted in their 2018 study [15] that CCL26 is responsible for gathering eosinophils in atopic conditions by engaging with CCR3 on asTh2 cells. This finding is consistent with previous studies that showed a significant increase in tissue eosinophilia and elevated expression of Th2 cytokines in most AD patients. Eosinophils, which are a type of white blood cells, are known to contribute to inflammation and allergic reactions, and their increased presence in AD lesions suggests a strong association between Th2 cell activation, chemokine production, and eosinophil infiltration.

Moreover, a study conducted by Furue et al.[16] in 2019 shed light on the origins of these chemokines. Their research showed that the chemokines CCL17, CCL18, and CCL22, which attract Th2 cells, are predominantly secreted by dendritic cells and various skin cells upon activation by asTh2 cell-derived cytokines, specifically IL-4 and IL-13. Meanwhile, CCL26 is produced by endothelial cells in response to stimulation by these same Th2 cytokines.. These findings underscore the close relationship between Th2 cells, chemokines, and the cellular environment in AD lesions. Renert-Yuval [17] in 2021 reinforced the importance of these eotaxins in AD pathogenesis, noting that CCL17, CCL18, CCL22, and CCL26 (another Th2-secreted chemokines) are overly expressed in the skin of AD patients. These findings highlight the potential therapeutic significance of targeting chemokines in the treatment of AD and offer insights into the complex interplay between asTh2 cells, chemokines, and other immune cells in the pathogenesis of atopic dermatitis.

3. Food Allergy

Food allergy refers to an unpleasant immune system reaction after the intake of a certain food. It is an atopic disease that primarily affects the digestive system. The Centers for Disease Control and Prevention estimate that food allergies impact between 4% to 6% of children and 4% of adults in the United States, while Cow's milk, hen's eggs, peanuts, wheat, soy, almonds, and fish are responsible for over 90% of food allergies in [18].

Research on the role of asTh2 cells in food allergies, especially peanut allergies, has been ongoing for years. Scientists revealed that allergic individuals have a higher number of food-responsive Th2 cells, which express high levels of IL-4, IL-5, and IL-13. Later in 2015 and 2018, the association of peanut allergy has been linked to a distinct group of highly specialized Th2 cells that produce IL-9 and IL-10 and carry the IL-25 receptor, known as IL17RB [19]. The expression of IL17RB suggests that these Th2 cells may be influenced by IL-25, a cytokine known to enhance asTh2 responses. This finding indicates that Th2 cells in peanut allergy might be part of a complex immune network contributing to allergic reactions.

Recent studies further explored the immune mechanisms underlying peanut allergies and the role of Th2 cells. For instance, Cardoso et al. [20] in 2019 studied STAT-6, a transcription factor that plays a key role in the signaling pathway of various cytokines, including those produced by Th2 cells. Their research demonstrated that STAT-6 is crucial for the development of Th2 inflammatory responses and intestinal damage related to peanut allergy. This emphasizes the significance of the STAT-6 signaling pathway in the immune response to peanuts, offering potential for targeted treatment.

In 2020, Ruiter et al. [20] analyzed the transcriptional profile of peanut-sensitized individuals with different reactivity thresholds. They found a unique expression pattern associated with Th2A (pro-allergic Th2) cells, responsible for allergic responses. Th2-associated genes, including IL4, IL13, and IL31, were highly expressed in these asTh2 cells. This suggests a higher presence of peanut-specific Th2A cells in reactive patients.

In conclusion, these studies highlight the central role of Th2 cells and associated signaling pathways in peanut allergy. Identifying key transcription factors such as STAT-6 and gene expression patterns linked to peanut-specific Th2 cells gives a deeper insight into the molecular mechanisms of peanut allergy. This knowledge could pave the way for targeted interventions and treatments to manage asTh2 cell responses and reduce peanut allergy symptoms.

4. Allergic asthma

Asthma is a prevalent chronic respiratory condition characterized by airway inflammation and bronchoconstriction, affecting individuals across various age groups. Emerging evidence suggests that Th2 cells play a pivotal role in allergic asthma pathogenesis, as indicated by multiple studies that have explored the underlying molecular and cellular mechanisms.

In 2017, Kuo et al. [22] undertook a transcriptomic analysis of sputum samples from asthmatic patients and identified a distinct gene expression cluster called TAC1, which they linked to Th2-mediated asthma. The TAC1 cluster was highly enriched in IL-13 and ILC2 gene signatures. Notably, the cluster also exhibited increased expression of IL33R and CLC proteins, which are associated with Th2 responses and eosinophil activation. It is likely that the IL33 axis may contribute to eosinophilic inflammation in allergic asthma through the release of IL-5, and IL-3.

In a separate study, Choy et al. [23] performed a comparative analysis of gene expression on lung tissue samples from individuals with asthma and the healthy. They discovered that CCL26, also known as eotaxin-3, stood out as the gene with the most significant difference in expression levels in those with asthma. CCL26 serves as a potent attractant for eosinophils by attaching to the CCR3 receptor. Notably, the production of CCL26 is significantly increased by IL-4 and IL-13 in human lung epithelial cells. This suggests a clear connection between Th2-related molecules, including CCL26, IL-5, and IL-13, and the Th2-type asthmatic inflammation.

In addition, Katoh et al. [24] explored the anti-inflammatory effects of Gal-9 in the allergic airway [30]. Gal-9 suppresses Th2 chemokines, including CCL11 and CCL17, thereby reducing inflammatory responses. Moreover, Gal-9 reduces Th2-associated airway inflammation by interacting with CD44, a molecule essential for recruiting T-cells inflammatory tissues and inhibiting the CD44-HA interaction that is vital for the movement of T-cells into the lung tissue.

In a meta-analysis, Demenais et al. [25] identified a susceptibility locus (rs20541) near IL13 and IL4 genes associated with Th2-associated asthma. This finding suggests that rs20541 may be a unique biomarker for allergen-specific Th2 cells in Th2-asthma. Furthermore, the association of rs20541 with IL-13 highlights IL-13's role in the production of IgE and the activation of the eosinophilic pathway in Th2-asthma pathogenesis. It also implies potential therapeutic applications through the development of anti-IL-13 agents.

In summary, Th2 cells play a central role in related asthma through a multitude of molecular and cellular pathways. Recent studies have identified key mediators and potential biomarkers, such as TAC1, IL-33, CCL26, Gal-9, and rs20541, which may offer novel targets for future asthma therapies.

5. Atopic rhinitis

Allergic rhinitis (AR) is a common inflammatory disorder of the upper airways, characterized by sneezing, runny nose, and red, watery, itchy eyes. It is another atopic disease associated with an elevated type 2 immune response caused by environmental allergen exposure in susceptible individuals.

Similar to other atopic diseases we have discussed, as Th2 cells involved in the pathogenesis of AR produce IL-4, IL-5, and IL-13 [26]. Additionally, AR-specific Th2 cells produce CCL17, which plays a role in attracting various immune cells, including eosinophils and more Th2 cells, to the site of inflammation. Researchers have noted higher levels of CCL17 in nasal secretions of AR patients, and these elevated levels are associated with the severity of the disease [27].

Thymic stromal lymphopoietin (TSLP) is a significant cytokine involved in the allergic response, with notable associations to Th2 cell activation and the onset of eosinophilic inflammation. TSLP emerges as a product of airway epithelial cells in response to environmental triggers, such as allergens, pollutants, and viral infections. The release of TSLP initiates a cascade of events whereby it stimulates dendritic cells. These dendritic cells, in turn, orchestrate the activation of Th2 cells and promote the synthesis of pivotal cytokines including IL-4, IL-5, and IL-13.[28].

It is important to note that while IL-4, IL-5, IL-13, CCL17, and TSLP are not solely unique to AR-specific Th2 cells, they are valuable in understanding the pathogenesis of AR. In particular, they can serve as potential therapeutic targets for the development of novel treatments for AR.

6. Conclusion

Allergen-specific Th2 cells play a central role in the pathogenesis of various atopic diseases, including atopic dermatitis, peanut allergy, allergic asthma, and atopic rhinitis. These cells contribute to the inflammatory response by producing cytokines such as IL-4, IL-5, IL-13, and IL-17RB, which are crucial for the development and maintenance of allergic symptoms. Biomarkers such as GATA3, Gal-9, and CCL26 have been identified as key indicators of Th2 cell activity and potential targets for therapeutic intervention. Further understanding the biological characteristics Th2 cells and their interaction with other cells within the microenvironment will provide valuable insights to aid the development of novel treatments and prevention strategies for atopic diseases.

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