Th2A cells: The pathogenic players in allergic diseases

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Proallergic type 2 helper T (Th2A) cells are a subset of memory Th2 cells confined to atopic individuals, and they include all the allergen-specific Th2 cells. Recently, many studies have shown that Th2A cells characterized by CD3+ CD4+ HPGDS+ CRTH2+ CD161high ST2high CD49dhigh CD27low play a crucial role in allergic diseases, such as atopic dermatitis (AD), food allergy (FA), allergic rhinitis (AR), asthma, and eosinophilic esophagitis (EoE). In this review, we summarize the discovery, biomarkers, and biological properties of Th2A cells to gain new insights into the pathogenesis of allergic diseases.

KEYWORDS allergic disease, Th2A cells, allergen-specific Th2 cells, HPGDS, CRTH2, CD161, ST2

Introduction

Allergic diseases are the greatest prevalent chronic immunological diseases, including AD, asthma, and AR, which are estimated to affect more than 230 million, 330 million, and 400 million people worldwide, respectively (1–3). The prevalence of allergic diseases is increasing in both industrial and developing countries, making it a global epidemic (4). Notably, people with allergic diseases are more likely to have a family disposition known as atopy, defined by Coca and Cooke in 1923 (5). Many studies show that the progression of allergic diseases occurs in a predictable time sequence and is widely distributed to various organs, which is referred to as the atopic march (6). It is known that AD and FA in infancy gradually develop into asthma and AR in childhood, even EoE (7). However, the mechanism of the atopic march remains unclear.

It is known that allergic diseases are mainly driven by type 2 inflammation, mediated by Th2 cells (8). When atopic individuals are exposed to allergens, their epithelial cells start to secrete IL-25, IL-33, and TSLP, leading to the activation of dendritic cells, which promote the differentiation of allergen-specific Th2 cells (9, 10). The activated allergen-specific Th2 cells can not only favor B cells to produce allergen-specific IgE, but also recruit and activate basophils, mast cells, and eosinophils by secreting IL-4, IL-5, and IL-13 (11, 12). Thus, allergen-specific Th2 cells play a crucial role in the allergic response.
Recently, pMHCII tetramer staining was widely used to study the allergen-specific Th2 cells (10, 13–17). However, the allergens in most allergic diseases are unclear. It is noted that Erik Wambre et al. defined a subset of memory Th2 cells confined to atopic individuals that include all allergen-specific Th2 cells as Th2A cells, which are characterized by CD4+ CRTH2+ CD161high HPGDS+ CD27low CD49dhigh ST2high, providing a novel approach to study the allergen-specific Th2 cells (18). Here, we review the discovery, biomarkers, and biological properties of Th2A cells to gain new insights into the pathogenesis of allergic diseases.

**Discovery of Th2A cells**

In type 2 inflammation, Th2 cells mainly trigger an inflammatory response, in which a subset of pathogenic effector Th2 cells (peTh2) are characterized by secreting high-level IL-5 cytokines (19, 20). After antigen elimination, most peTh2 cells are induced to undergo cell apoptosis, and part of them differentiate into memory-type Th2 cells (21). The memory-type Th2 cells in allergic diseases are activated by exposure to various allergens, which contribute to the recurrence of diseases. For instance, Kurokawa et al. demonstrate that the expression of ST2 in T cells is responsible for the pathogenesis of asthma (22). In addition, Calman Prussin et al. found that IL-5+ Th2 cells are highly differentiated Th2 cells that demand repetitive allergen exposure to generate, demonstrating that Th2-dominant diseases characterized by recurrent allergen stimulation possibly promote the generation of IL-5 Th2 cells, leading to the occurrence of eosinophilic inflammation (23). Moreover, Mitson et al. found that the CRTH2+ CD161high HPGDS+ memory Th2 cells play a central role in AD and eosinophilic gastrointestinal disease (EGID) (20). Numerous studies demonstrate that the CD45ROhigh CD69high ST2high IL17RBhigh memory Th2 cells are the primary pathogenic subset in eosinophilic chronic rhinosinusitis (24–26). Meanwhile, Stephen Till et al. proposed that IL-17RB+ CD4+ Th2 cells may represent a subset that co-expresses ST2 during activation and may be pathogenic for chronic rhinosinusitis with nasal polypsis via the IL-25/IL-33 axis (27).

In 2012, Wambre et al. found the pathogenicity of allergen-specific CD4+ T cells to be associated with the CRTH2+ CD27low phenotype (13). Wambre et al. proposed the Th2A cells, which can evaluate the severity of allergic diseases and the therapeutic effect of the allergen-specific immunotherapy (AIT) (28). In 2015, Wambre et al. clarified the importance of Th2A cells for allergic diseases and the possibility of Th2A cells as a target in AIT (29). Importantly, in 2017, Wambre et al. defined a subset of memory Th2 cells confined to atopic individuals that include all allergen-specific Th2 cells as Th2A cells, characterized by the expression of CD4+ CRTH2+ CD161high HPGDS+ CD27low CD49dhigh ST2high (18). Wambre et al. discovered that expression of a cardinal Th2 cytokine by peanut-reactive T cells was mainly restricted to allergic individuals and the Th2A cell subset and that a decrease in Th2A cells is also associated with peanut desensitization, confirming that Th2A cells are involved in the pathogenesis of FA (18, 30–32). Chiang et al. found the heterogeneity of effector Th2 subsets in food allergies (33). On the other hand, Renand et al. show that a decrease in grass pollen-specific CD4+ T cell frequency most closely paralleled the transient clinical outcome of allergen immunotherapy via either the subcutaneous or sublingual route (34). In 2020, Luce et al. found a decrease in Th2A cells after a period of food oral immunotherapy (OIT), but the frequency of DCs and ILCs remained, confirming the possibility of Th2A frequency as a new marker for OIT (35). In 2021, Bangert et al. found that Th2A cells were persistently maintained in the tissues of AD patients, suggesting that Th2A cells may be responsible for AD recurrence (36). Meanwhile, Luce et al. observed the frequency of CD38+ Th2A cells to be only significantly decreased in patients who received the treatment of HDM tablets, demonstrating the potential value of CD38+ Th2A cells as the new biomarker of asthma (37). In the meantime, Morgan et al. found that Th2A cells are enriched in esophageal tissue from EoE patients and associated with the recruitment of eosinophils to the esophageal tissue, indicating that Th2A cells are the pathogenic cells for EoE (38). A recent study by Vandamme et al. using TCR and transcriptomic analysis of dog allergen-specific T cell responses in allergic subjects revealed a close relationship between Th2-like, Th2, and Th2A cells (39).

**Biomarkers of Th2A cells**

**HPGDS**

Unlike conventional Th2 cells, Th2A cells have a high expression of hematopoietic prostaglandin D2 synthase (HPGDS). HPGDS is a glutathione transferase expressed mainly in mast cells and antigen-presenting cells (40). Upon the stimulation of allergens, arachidonic acid is liberated from phospholipids under the mediation of phospholipase A2 (PLA2), and some arachidonic acid can be transformed into PGH2 by the action of COX (41). HPGDS then catalyzes the conversion of arachidonic acid–derivative PGH2 to PGD2 with the assistance of GSH and Mg2+ (42). PGD2 acts on the G-protein coupled receptor DP1 and receptor DP2/CRTH2 expressed in Th2 cells to promote inflammation by the action of IL-4, IL-5, and IL-13 cytokines (43) (Figure 1). Thus, the high-level expression of HPGDS in Th2A cells helps to promote the type 2 inflammatory response. The study shows that the HPGDS inhibitor improved AD symptoms, possibly due to a reduction in PGD2 production, indicating that HPGDS...
might be a potential therapeutic target for allergic diseases (44, 45).

**CRTH2**

The chemoattractant receptor homologous molecule expressed on T-helper-type-2 cells (CRTH2) is a g-protein–coupled receptor of prostaglandin (PG) D2, mainly expressed in Th2 cells, eosinophils, basophils, and ILC2 (46–48). Many studies show that CRTH2 is one of the biomarkers of Th2A cells (18, 20). The combination of CRTH2 with PGD2 can induce the chemotaxis of Th2 cells, basophils, and eosinophils, recruiting circulating inflammatory cells from blood vessels to the site of inflammation (49–51). CRTH2 activated by PGD2 restraints adenylyl cyclase (AC) activity through the Gα protein subunit, reducing the intracellular cAMP level, which can reduce the transcriptional activity of NF-κB and induce the phosphorylation of CREB protein to inhibit inflammation (52, 53). CRTH2 also activates the Gβγ complex to provoke the formation of PIP2 hydrolyzed by phospholipase Cβ, leading to the production of DAG and IP3 (52, 54). DAG can activate PKCβ and the MAPK/ERK pathway, activating the transcription factors NF-κB and AP-1, respectively (55). IP3 can induce the release of Ca2+ from the endoplasmic reticulum to activate transcription factor NFAT by the phosphatase calcineurin (52, 55) (Figure 1). As is known, CRTH2 is a significant marker of ILC2, which promotes the effector function in ILC2 (48). More importantly, the activation of CRTH2 stimulates Th2 cells to produce IL-4, IL-5, and IL-13 (56, 57). Moreover, CRTH2+ Th2 cells express more CD200R, which strongly correlates with Th2A pathology (58, 59).

**CD161**

CD161, namely, NKR-P1, is a C-type lectin-like receptor mainly expressed in ILC2, NK cells, TH17 cells, and circulating memory T cells (48, 60). As the most significant biomarker in Th2A cells, CD161 is commonly regarded as the co-signaling
receptor in T cells, the expression of which is related to memory phenotype (61). The binding of CD161 to LLT1 may recruit aSMase, which can upregulate Bcl-XL expression by mediating IL-2 secretion, resulting in the reduction of susceptibility to apoptosis, leading to the prolonged survival of effector memory T cells (62, 63). More importantly, aSMase catalyzes sphingomyelin (SM) to generate ceramide (64) (Figure 1). Ceramide aggregates into a platform, which leads to the permeability alternation of the membrane (65–68). Intracellular ceramide affects the multifarious cellular processes and protein kinase activation (Ras/PKC), mediating the Akt-mTOR and MAPK cellular pathways downstream of CD28 and CD3 to regulate cell apoptosis, proliferation, and differentiation (62, 69, 70). Similar to Th2A, CD161 and CRTH2 co-expression are characteristic of ILC2 as well (48).

ST2

Serum stimulation-2 (ST2), known as IL1RL1, is an orphan receptor mainly expressed in Th2 cells, Treg cells, Th9 cells, and ILC2s (71, 72). ST2 expression on peripheral allergen-specific CD4+ T cells is confined to allergy individuals and restricted to Th2A cells and, on circulating CD4+ T cells, represents a transient phenotype associated with Th2A cell activation, allowing these cells to sense locally elicited tissue cytokines (73, 74). ST2 exists in two ways, which are different in signal transduction: a membrane-bound form and a soluble form (sST2) (71). After ST2 binds to its only ligand IL-33, the myeloid differentiation factor 88 (MyD88) is recruited to the intracellular domain, activating TRAF6 signaling via IL-1R-associated kinase (IRAK) (71, 75). Downstream MAPK kinases and the IKK complex activated by TRAF6 regulate the activation of AP-1 and the release of NF-kB from the complex, respectively (72) (Figure 1). However, sST2 inhibits IL-33/ST2 signaling by isolating free IL-33 (71). IL-33 selectively amplifies pathogenic Th2 cell effector functions, suggesting a tissue checkpoint that may regulate adaptive allergic immunity (73). Many studies show that ST2 in Th2A cells presents a transient phenotype related to cell activation, leading to the expression of IL-5 and IL-13 (71, 73, 76).

PPAR

Peroxisome proliferator–activated receptor (PPAR) is a member of the nuclear receptor superfamily that is mainly expressed on macrophages and Th2A cells (77, 78). Activated PPAR forms a heterodimer with the retinoid X receptor (RXR), which can combine with the upstream PPAR response element to regulate the transcription of the target genes included in adipogenesis, lipid metabolism, inflammation, and metabolic homeostasis (79). PPARγ can directly regulate the generation of IL-5 and the expression of ST2 both in vitro and in vivo (80). As mentioned, the IL-33/ST2 axis can strongly accelerate the Th2 cell function, indicating that PPARγ might be a potential target for the treatment of allergic diseases (73, 80).

Biological properties of Th2A cells

In the type 2 inflammatory response, epithelial cells and keratinocytes secrete IL-25, IL-33, and TSLP to activate ILC2, APCs, and Th2A cells, which induce the Th2 response to secrete IL-4, IL-5, IL-9, IL-10, and IL-13 in response to allergen stimulation (10, 11, 48). It is known that Th2A cells play a significant role in allergic diseases, but the mechanism remains unclear (18). We believe that, after exposure of atopic individuals to allergens, APCs present allergens to the tissue-resident Th2A cells, inducing cell activation (81). The activated Th2A cells may produce IL-5 and IL-9 to favor the recruitment and activation of eosinophils, which is supported by the fact that the Th2A subset presents a significant positive correlation with the number of eosinophils in the peripheral blood of atopic individuals (19, 20, 82). Meanwhile, Th2A cells may secrete IL-4 and IL-13, stimulating B cells to produce allergen-specific IgE antibodies that sensitize mast cells and basophils (11). In addition, Th2A cells may produce IL-4, IL-9, and IL-10 to activate the sensitized mast cells and basophils (11) (Figure 2). PGD2 secreted by the activated mast cells, in turn, acts on CRTH2 in Th2A cells, further promoting the activation of Th2A cells (83). Besides this, Th2A cells can survive in the tissues and blood for years, reserving the ability of allergen memory (73). Notably, ILC2s can induce tissue repair and result in the recruitment and activation of eosinophils and mast cells, which are functionally like Th2A cells and also essential to triggering the type 2 response but differ in that ILC2s have no TCR and allergen specificity (19, 84).

Th2A cells in Allergic Diseases

Th2A cells in AD

AD is the most common chronic inflammatory skin disease characterized by severe pruritus, recurrent eczema, and fluctuating course, which would gradually develop into FA, asthma, and even EoE (1). In 2021, Bangert et al. analyzed samples from the antecubital fossa of AD patients who had received the treatment of IL-4Rα blockers for 16 weeks and a year with single-cell RNA sequencing (scRNA-seq). Notably, a cluster of cells with IL17RB+ CRTH2+ CD161+ CD27low phenotype most in accord with Th2A cells was found in the tissues of AD patients. Moreover, it is shown that even after a year of treatment, Th2A cells persistently existed in the patient tissues but were not present in healthy skin, indicating that Th2A cells are the main pathogenic subset for AD, possibly resulting in recurrent AD (36).
Th2A cells in FA

FA is an adverse immune response induced by food allergens, including peanuts, milk, soy, and fish et al. (85, 86). Studies indicate that FA is caused by allergen-specific TH2 cells through the mediation of IgE switching and expansion of lymphocytes (87). Wambre et al. completed a longitudinal study on patients with peanut allergies who underwent characterized oral desensitization immunotherapy in 2017 (CODIT). In this randomized, double-blind, placebo-controlled experiment, most of the CD4+ T cells responding to peanuts were verified to be Th2A cells by a CD154 upregulation assay, which can observe the quantity of peanut-specific T cells in vitro. Furthermore, it is shown that a decrease in Th2A cell frequency is positively correlated with peanut desensitization, demonstrating the association of Th2A cells with the pathogenesis of FA (18). In 2020, Luce et al. recruited 60 desirable patients to be treated with omalizumab at weeks 1 to 16 and multi-OIT that included two to five kinds of allergens at weeks 8 to 30, and the patients received a food challenge at week 30. Fluorescent antibody labeling revealed a decrease in Th2A cell frequency at week 30 compared with the baseline. Inversely, no changes in ILC and DC frequency were observed through flow cytometry, indicating the value of Th2A frequency as a new marker for OIT (35). Meanwhile, Monian et al. subdivided the observed cells into six subsets through single-cell RNA-Seq and paired T cell receptor α/β sequencing, where inhibition of the Th2 signature in the Th2A subpopulation correlates with clinical outcomes of OIT (32). Moreover, Chiang et al. discovered that Tregs activated by IL-2 could partially inhibit the Th2 response, but the heterogeneous Th2 response was not significantly inhibited (33). Then, Lozano-Ojalvo found that IL-2 produced by allergen-specific cells can induce the activation of Treg cells with suppressive properties during an oral food challenge (88). In 2022, Bajzik et al. demonstrated that, during an experiment, the Th2A cell level observed in the peripheral blood of peanut-allergic patients is associated with not only T-cell reactivity to peanuts but also serum peanut-specific IgE and IgG4 levels (89).

Th2A cells in Asthma

Asthma is a chronic allergic inflammatory disease characterized by multiple respiratory symptoms, airflow limitation, and reversible airflow obstruction (2). A study was performed in 2021 by Luce et al. on 182 patients with allergies to house dust mites (HDM) to indicate the role of Th2A cells in allergic diseases. During the randomized, double-blind, placebo-controlled trial, these patients were treated with daily either 300 IR (n = 58), 500 IR (n = 63) HDM, or placebo (n = 61) tablets for 12 months. Flow cytometry was used to examine the changes in Th2A cell frequency between baseline
and the end of AIT. Because both the active and placebo groups showed a decrease in Th2A cells, the same analysis was performed with CD38, which is upregulated in Th2A cells. The results suggest that a significant reduction in CD38⁺ Th2A was observed only in all active groups, confirming the potential value of CD38⁺ Th2A cells as the new clinical biomarker of asthma (37). Meanwhile, Rilnova, EA et al. observed that, after treatment, the proportion of Th2A in Th2 cells decreased in the peripheral blood of asthma patients (90). Interestingly, in the ovalbumin-induced asthma mouse model, the expression of pathogenic Th2 cells in ST2−/− and IL33−/− mice is reduced significantly compared with ST2+/+ and IL33+/+ mice, resulting in observable improvement of pulmonary fibrosis, collagen deposition, and the prominent decrease in fibrosis-related gene expression, which indicates that ST2hi memory pathogenic Th2 cells are involved in the establishment of airway fibrosis (91).

Th2A cells in EoE

EoE is a chronic esophageal inflammatory disease characterized by pathological eosinophil infiltration, leading to dysphagia, food impaction, and impaired esophagus function (92, 93). In 2019, Rothenberg et al. utilized scRNA-seq to discover the specific enrichment of HPGDS⁺ CRTH2⁺ IL-17RB⁺ FFAR3⁺ CD4⁺ Th2 cell in EoE (94). In 2021, Morgan et al. collected biopsy tissue from the esophagus and duodenum of 10 patients with EoE (n = 6 active disease, n = 4 remission disease) and enzymatically hydrolyzed the patient tissues into a single-cell suspension for scRNA-seq. Th2A cells were prominently higher in the patients with active diseases due to the calculation of the two-sided Wilcoxon rank-sum test and enriched in the esophageal tissue of patients with EoE. In addition, the result of ligand-receptor pathway analysis shows that receptors selectively expressed on eosinophils are matched with the ligands on Th2A cells, indicating that Th2A cells may be related to the recruitment of eosinophils to the esophageal tissue (38).

Immunotherapy targeting Th2A cells

It is known that, with insight into the immune mechanism, many targeted drugs are now applied to treat moderate and severe allergic diseases. As Th2A cells are pathogenic for allergic diseases, relative monoclonal antibodies are widely used, such as IL-4 monoclonal antibody (Pitrakinra, Dupilumab) (95–97), IL-5 monoclonal antibody (Mepolizumab, Reslizumab, Benralizumab) (98), IL-9 monoclonal antibody (MEDI-528) (99), IL-13 monoclonal antibody (Lebrikizumab, Tralokinumab) (100, 101), IL-33 monoclonal antibody (Etokimab, AMG 282) (102, 103), TSLP monoclonal antibody (Tezepelumab) (104), and IgE monoclonal antibody (Omalizumab, Ligelizumab) (105, 106). Importantly, JAK can regulate the full activation of Th2A cells, thus, JAK inhibitors also play an indispensable role in allergic disease treatment (107–114) (Table 1).

Moreover, Th2A cells have the possibility to be deleted selectively. Studies demonstrate that a persistent high dose of allergen cumulation in AIT might lead to the selective functional

| Target | Agent Name | Indications | Status | Reference |
|--------|------------|-------------|--------|-----------|
| IL-4   | Pitrakinra | asthma      | Phase 2| (95)      |
|        | Dupilumab  | AD, asthma, EoE | FDA-approved | (96, 97) |
| IL-5   | Mepolizumab| asthma      | FDA-approved | (98)     |
|        | Reslizumab | asthma      | FDA-approved | (98)     |
|        | Benralizumab| asthma, EoE | FDA-approved | (98)     |
| IL-9   | MEDI-528  | asthma      | Phase 2| (99)      |
| IL-13  | Lebrikizumab| AD, asthma | Phase 3| (100, 101)|
|        | Tralokinumab| AD, asthma | Phase 3| (100)     |
| IL-33  | Etokimab (ANB020)| AD, asthma, peanut allergy | Phase 2| (102)    |
|        | AMG 282   | chronic rhinosinusitis with nasal polyps, asthma | Phase 1| (103)    |
| TSLP   | Tezepelumab| asthma      | Phase 3| (104)     |
| IgE    | Omalizumab | asthma      | Phase 3| (105)     |
|        | Ligelizumab| asthma      | Phase 3| (106)     |
| JAK1   | Upadacitinib| AD         | Phase 3| (107)     |
|        | Abrocitinib| AD         | FDA-approved | (108)   |
|        | Oclacitinib| Canine AD  | FDA-approved | (109)   |
| JAK1/2 | Baricitinib| AD         | FDA-approved | (110, 111)|
| JAK1/JAK2/JAK3/TYK2 | Delgocitinib | AD | Phase 3| (112)     |
|        | Gusacitinib| AD         | Phase 1| (113)     |
deletion of proallergic Th2 cells, which permits the occurrence of other T cell responses (29). Moreover, this chronic stimulation of high-dose allergens may induce autocrine IL-10 generation, which is the salient mediator of T cell exhaustion and the methylation of the GATA-3 promoter related to the decrease in Th2 cell activity (115, 116).

Conclusion

Th2A cells are a subset of memory Th2 cells confined to atopic individuals, including all the allergen-specific Th2 cells. Notably, Th2A cells are characterized by the expression of CD4+ CRTH2+ CD161hi HPGDS+ CD27low CD49dhi ST2hi, which exhibit multiple biological properties leading to cell survival, activation, and cytokine secretion. After allergen exposure, APCs involve in allergen presentation to activate Th2A cells which can secrete IL-4, IL-5, IL-9, IL-10, and IL-13, leading to the activation of mast cells, basophils, and eosinophils. It is known that Th2A cells are demonstrated to be the central pathogenic cells in various allergic diseases, including AD, FA, asthma, and EoE. The frequency of Th2A cells can be used to assess the efficacy of allergic disease treatment, and selective Th2A cell deletion may result in long-term clinical benefits. Subsequently, Th2A cells are expected to be the focal point of research into the pathogenesis of allergic diseases and a critical target for disease treatment.

Author contributions

ZH wrote most of the review. ZH and MC contributed to writing and correcting the manuscript. XC, ZW, LJ, and YM participated in critically correcting the manuscript. MC and YW contributed to the manuscript structure and supervised the work.

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Conflict of interest

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References

1. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet (2020) 396 (10247):345–60. doi: 10.1016/S0140-6736(20)31286-1
2. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet (2018) 391 (10122):783–800. doi: 10.1016/S0140-6736(17)33511-1
3. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet (2011) 378(9789):2112–22. doi: 10.1016/S0140-6736(11)60130-X
4. Rutkowski K, Sowa P, Rutkowski-Talipska J, Sulkowski S, Rutkowski R. Allergic diseases: the price of civilizational progress. Adv Dermatol Allergology/ Postepy Dermatologii i Alergologii (2014) 31(2):77. doi: 10.5144/pdia.2014.40936
5. Ring J. Terminology of allergic phenomena. Chem Immunol Allergy (2014) 100:46–52. doi: 10.1159/000385500
6. Yang L, Fu J, Zhou YF. Research progress in atopic march. Front Immunol (2020) 11:1907. doi: 10.3389/fimmu.2020.01907
7. Aw M, Penn J, Gauvreau GM, Lima H, Sehmi R. Atopic march: collegium international allergologico update 2020. Int Arch Allergy Immunol (2020) 181 (1):1–0. doi: 10.1159/000502958
8. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discovery (2016) 15(1):33–50. doi: 10.1038/nrd4624
9. Saez SA, Taylor BC, Artsi D. Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. Immunol Rev (2008) 226:172–90. doi: 10.1111/j.1600-065X.2008.00713.x
10. Wambre E, James EA, Kwok WW. Characterization of CD4+ T cell subsets in allergy. Curr Opin Immunol (2012) 24(6):700–6. doi: 10.1016/j.coi.2012.07.009
11. Romagnani S. The role of lymphocytes in allergic disease. J Allergy Clin Immunol (2000) 105(3):399–408. doi: 10.1067/mai.2000.104575
12. Teran LM, Chemokines and IL-5: major players of eosinophil recruitment in asthma. Clin Exp Allergy: J Br Soc Allergy Clin Immunol (1999) 29(3):287–90. doi: 10.1046/j.1365-2222.1999.00522.x
13. Wambre E, DeLong JH, James EA, LaFond RE, Robinson D, Kwok WW. Differentiation stage determines pathologic and protective allergic-specific CD4+ T-cell outcomes during specific immunotherapy. J Allergy Clin Immunol (2012) 129:544–51. doi: 10.1016/j.jaci.2011.08.034
14. Macaubas C, Wahlstrom J, da Silva APG, Forsthuber TG, Sønderstrup G, Kwok WW, et al. Allergen-specific MHCI class II tetramer+ cells are detectable in allergic, but not in nonallergic, individuals. J Immunol (2006) 176(8):5069–77. doi: 10.4049/jimmunol.176.8.5069
15. Wambre E, DeLong JH, James EA, Torres-Chinn N, Plätzner W, Möbs C, et al. Specific immunotherapy modifies allergen-specific CD4+ T-cell responses in an epitope-dependent manner. J Allergy Clin Immunol (2014) 133(3):872–9.e7. doi: 10.1016/j.jaci.2013.10.054
16. Archila I, DeLong J, Wambre E, James E, Robinson D, Kwok W. Grass-specific CD4+ T-cells exhibit varying degrees of cross-reactivity, implications for allergen-specific immunotherapy. Clin Exp Allergy (2014) 44(7):986–98. doi: 10.1111/cea.12324
TH17 signature in nasal mucosa.

Huang et al. 10.3389/ Frontiers in Immunology frontiersin.org 08

113(20):E2842

airway.

interleukin-33-p38 kinase axis confers memory T helper 2 cell pathogenicity in the memory T-helper cells in allergic airway in

CD38+ TH2A cell frequencies following immunotherapy with house dust mite

eabe2749. doi:10.1126/sciimmunol.abe2749

resolved atopic dermatitis under IL-4R

Persistence of mature dendritic cells, TH2A, and Tc2 cells characterize clinically

frequencies and regulatory marker as follow-up biomarker candidates for successful multifocal oral immunotherapy. Allergy (2020) 75(6):1513.

Banger C, Rindler K, Krausgruber T, Alkon N, Thaler FM, Kurz H, et al. Persistence of mature dendritic cells, TH2A, and Tc2 cells characterize clinically

resolved atopic dermatitis under IL-4R blockade. Sci Immunol (2021) 6(55):

sub2749. doi:10.1126/sciimmunol.ab2749

Luce S, Batard T, Bordas-Le Flech V, Le Gall M, Mascarel L. Decrease in CD8+ TH2A cell frequencies following immunotherapy with house dust mite tablet correlates with humoral responses. Clin Exp Allergy (2021) 51(8):1057–68. doi: 10.1111/cea.13891

38. Morgan DM, Ruiter B, Smith NP, Tu AA, Monian B, Stone BE, et al. Clonally expanded, GPR15-expressing pathogenic effector TH2 cells are associated with eosinophilic esophagitis. Sci Immunol (2021) 6(62): eabj5586. doi: 10.1126/sciimmunol.abj5586

39. Vandamme C, Rytkonen-Nissinen M, Lönngren T, Randell J, Harvima RI, Kinnunen T, et al. Single-cell characterization of dog allergen-specific T cells reveals TH2 heterogeneity in allergic individuals. J Allergy Clin Immunol (2022) 149(5):1732–43.e15. doi: 10.1016/j.jaci.2021.11.018

40. Kanaoka Y, Urade Y. Hematopoietic prostatesarglandin d synthase. Prostaglandins Leukotrienes Essential Fatty Acids (2003) 69(2-3):163–7.

41. Urade Y. Biochemical and structural characteristics, gene regulation, physiological, pathological and clinical features of lipocalin-type prostatesarglandin d synthase as a multifunctional lipocalin. Front Physiol (2021) 12. doi: 10.3389/fphys.2021.71802

42. Inoue T, Irikura D, Okazaki N, Kinugasa S, Matsumura H, Uodome N, et al. Mechanism of metal activation of human hematopoietic prostaglandin d synthase. Nat Struct Bio (2003) 10(4):291–6. doi: 10.1016/S0969-490X(03)00027-9

43. Rittchen S, Heinemann A. Therapeutic potential of hematopoietic prostatesarglandin d2 synthase in allergic inflammation. Cells (2019) 8(6):619.

44. Hau CS, Kanada N, Watanabe S. Suppressive effects of antiimmunocytes on thrym sternal lymphopoeitin production in human keratinocytes. J Dermatol Sci (2013) 71(3):174–83. doi: 10.1016/j.jdermsci.2013.04.023

45. Hirai H, Tanaka K, Yoshie O, Ogawa K, Kenmotsu T, Takamori Y, et al. Prostaglandin D2 selectively induces chemotaxis in TH2 helper type 2 cells, eosinophils, and basophils via seven-transmembrane receptor CRTH2. J Exp Med (2001) 193(2):255–62. doi: 10.1084/jem.193.2.255

46. Nagata K, Hirai H, Tanaka K, Ogawa K, Aso T, Sugamata K, et al. CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast-cell-derived factor(s). FEBS Letters (1999) 469(2):195–9. doi: 10.1016/S0014-5793(99)01251-x

47. Hazenberg MD, Spits H. Human intracellular lymphocytes. Blood (2014) 124(5):709–9. doi: 10.1182/blood-2013-11-427781

48. Gyles SL, Xue L, Townsend ER, Wettby F, Pettipher R. A dominant role for chemotaxin receptor-homologous molecule expressed on T helper type 2 (Th2) cells (CRTH2) in mediating chemotaxis of CRTH2+ CD4+ Th2 lymphocytes in response to mast cell supernatants. Immunology (2006) 119(3):362–8. doi: 10.1111/j.1365-2664.2006.04840.x

49. Nagata K, Hirai H. The second PGD2 receptor CRTH2: structure, properties, and functions in leukocytes. Prostaglandins Leukotrienes Essential Fatty Acids (2002) 69(3):169–77. doi: 10.1054/jpes.2002.300074

50. Marone G, Galdiero MR, Pecoraro A, Pucino V, Criscuolo G, Triassi M, et al. Prostaglandin D2 receptor antagonists in allergic disorders: safety, efficacy, and future perspectives. Expert Opin Investigational Drugs (2019) 28(1):73–84. doi: 10.1080/13543784.2019.1555237

51. Kostenis E, Ulven T. Emerging roles of DP and CRTH2 in allergic inflammation. Trends Mol Med (2006) 12:148–58. doi: 10.1016/j.molmed.2006.02.005

52. Tavares LP, Negrerieo-Lima GL, Lima KM, Silva PM, Pinho V, Teixeira MM, et al. Blame the signaling. Role of CAMP for the resolution of inflammation. Pharmacol Res (2020) 159:101503. doi: 10.1016/j.phrs.2020.101503

53. Xue L, Gyles SL, Wettby FR, Gazi I, Townsend E, Hunter MG, et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemotaxin receptor-like receptor on Th2 cells. J Immunol (2005) 175(10):6531–6. doi: 10.4049/jimmunol.175.10.6531

54. Gaud G, Lesorune R, Love PE. Regulatory mechanisms in T cell receptor signalling. Nat Rev Immunol (2018) 18(5):485-97. doi: 10.1038/s41577-018-0020-8

55. Kupczyk M, Kuna P. Targeting the PGD2/CRTH2/DP1 signaling pathway in asthma and allergic disease: current status and future perspectives. Drugs (2017) 77(12):1281–94. doi: 10.1007/s40265-017-0777-2

56. Xue L, Barrow A, Pettipher R. Interaction between prostaglandin D2 and chemotaxin receptor-homologous molecule expressed on Th2 cells mediates cytokine production by Th2 lymphocytes in response to activated mast cells. Clin Exp Immunol (2009) 156(1):126–33. doi: 10.1111/j.1365-2446.2008.03871.x

57. Blom LH, Martel BC, Larsen LF, Hansen CV, Christensen MP, Juel-Berg N, et al. The immunoglobulin superfamily member CD208R identifies cells involved in type 2 immune responses. Allergy (2017) 72(7):1081–90. doi: 10.1111/all.13343

58. Wambre ER, Farrington M, Baizik V, Delberg HA, Ruddy M, DeVeaux M, et al. Clinical and immunological evaluation of cat-allergic asthmatics living with or without a cat. Clin Exp Allergy (2021) 51(12):1624–33. doi: 10.1111/cea.14024
in dendritic cells and enhances Th2 immune responses.

Huang et al. J Exp Med 2016; 213(4):1323–23. doi: 10.1084/jem.20151383

Adam D, Heinrich M, Kabelitz D, Schütze S. Ceramide: does it matter for T cells? Cell Death Disease (2012) 42(12):1745–56. doi: 10.1038/cddis.2012.283

Tischer D, Thees J, Karabinskaya A, van den Brandt J, Reichardt SD, Karow U, et al. Acid sphingomyelinase is required for protection of effector memory T cells against glucocorticoid-induced cell death. J Immunol (2011) 187(9):4509–16. doi: 10.4049/jimmunol.1100911

Zidan YH, Hannan YA. The acid sphingomyelinase/ceramide pathway: biomedical significance and mechanisms of regulation. Curr Med Chem (2010) 17(5):545–66. doi: 10.2174/10221241010050808225

Bollinger CR, Teichgräber V, Gulbins E. Ceramide-enriched membrane domains. Biochim Biophys Acta (BBA)-Molecular Cell Res (2005) 1746(3):284–94. doi: 10.1016/j.bbamcr.2005.09.001

Grassme H, Jolde S, Riehle A, Schwarz H, Berger J, Sandhoff K, et al. CD95 signaling via ceramide rich membrane rafts. J Biol Chem (2001) 276(23):20589–96. doi: 10.1074/jbc.M102172000

Gulbins E. Regulation of death receptor signaling and apoptosis by ceramide. Pharmacol Rev (2001) 43(5):393–49. doi: 10.1124/pr.43.5.9

Gulbins E, Kolesnick R. Raft ceramide in molecular medicine. Oncogene (2003) 22(33):7077–70. doi: 10.1038/sj.onc.1207146

Pozzo D, Vales-Gómez M, Mavadat N, Williamsson SC, Chisholm SE, Reyburn H. CD161 (human NK-P1A) signaling in NK cells involves the activation of acid sphingomyelinase. J Immunol (2006) 176(4):2397–406. doi: 10.4049/jimmunol.176.4.2397

Bai A, Guo Y. Acid sphingomyelinase mediates human CD4+ T-cell biomarker. J Immunol (2003) 220(10):2779–85. doi: 10.4049/jimmunol.220.10.2779

van Dyken SJ, Nusbaum JC, Lee J, Molófsky AB, Liang H-E, Pollack JL, et al. A tissue checkpoint regulates type 2 immunity. Nat Immunol (2016) 17(3):373–82. doi: 10.1038/ni.3582

Grässner A, Baczynska S. The ST2/LIL3 axis in immune cells during inflammatory diseases. Front Immunol (2017) 8. doi: 10.3389/fimmu.2017.00475

Baumann C, Bonilla WV, Fröhlich A, Helmstetter C, Peine M, Hegazy AN, et al. A tissue checkpoint regulates type 2 immunity. Proc Natl Acad Sci USA (2015) 112(3):4056–61. doi: 10.1073/pnas.1410854112

Calise J, Garabatos N, Bajzik V, Farrington M, Robinson D, Jeong D, et al. Single-cell RNA sequencing identifies inflammatory tissue in eosinophilic cells. J Clin Invest (2019) 129(5):2014–24. doi: 10.1172/JCI125971

Hambly N, Nair P. Monoclonal antibodies for the treatment of refractory asthma. Curr Opin Pulm Med (2014) 20(1):87–94. doi: 10.1097/MCP.00000000000000007

Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. J-STAT4-dependent IL-33 receptor expression directly promotes antiviral Th2 responses. Proc Natl Acad Sci USA (2015) 112(3):4056–61. doi: 10.1073/pnas.1410854112

Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. J-STAT4-dependent IL-33 receptor expression directly promotes antiviral Th2 responses. Proc Natl Acad Sci USA (2015) 112(3):4056–61. doi: 10.1073/pnas.1410854112

Optimal human pathogenic TH2 cell effector function requires local epithelial cacy during grass pollen sublingual immunotherapy. J Allergy Clin Immunol (2008) 7(10):827–34. doi: 10.1016/j.jaci.2008.07.026

Dharamsi Z, Smith I, Vyas S, Pillai G, Verhulst T, De Meyer S, et al. Single-cell RNA sequencing identifies inflammatory tissue in eosinophilic cells. J Clin Invest (2019) 129(5):2014–24. doi: 10.1172/JCI125971

Blinova EA, Galdina VA, Pashkina VA, Makarova AE, Demina DV, Koulou VA. Proportion of TH2A/Th2 cells in the peripheral blood of patients with asthma decreases after therapy. Allergy: European Journal of Allergy and Clinical Immunology Supplement (2021) 765(113):133. doi: 10.1111/all.15095

Asthma, Atopy, and Allergy. J Allergy Clin Immunol (2010) 125(2):S116–25. doi: 10.1016/j.jaci.2009.08.028

Kraml M, Luedtke M, Lauterbach C, Ziegler S, Weidinger S, Nowak C, et al. Allergen recognition by specific effector Th2 cells enables IL-2-dependent activation of regulatory T cell responses in humans. medRxiv (2022). doi: 10.1101/2022.05.17.2227017

Yi A, Tay TR, Choo X, Koh M, Tee A, Wang DY. Precision medicine in united airways disease: a “treatable traits” approach. Allergy (2018) 73(10):1964–78. doi: 10.1111/all.13496

Lozano-Ojábal D, Tyler SR, Aranda CJ, Wang J, Schierer SH, Sampson HA, et al. Adverse reactions to food: Position paper of the European academy of allergology. Allergy: European Journal of Allergy and Clinical Immunology (2017) 72:1693–1703. doi: 10.1111/all.13595

Bischoff SC. Role of mast cells in allergic and non-allergic inflammatory diseases. Front Immunol (2020) 11:14. doi: 10.3389/fimmu.2020.00129

Todesillas L, Berin MC, Sampson HA. Immunology of food allergy. Immunity (2017) 47(1):32–50. doi: 10.1016/j.immuni.2017.07.004
responses. J Allergy Clin Immunol (2016) 138(4):1051–9. doi: 10.1016/j.jaci.2016.02.027

107. Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller A, Barbarot S, et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatology (2021) 157(9):1047–55. doi: 10.1001/jamadermatol.2021.3023

108. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and safety of oral janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. JAMA Dermatol (2019) 155(12):1371–9. doi: 10.1001/jamadermatol.2019.2855

109. Cosgrove SB, Wren JA, Cleaver DM, Walsh KE, Follis SI, King VI, et al. A blinded, randomized, placebo-controlled trial of the efficacy and safety of the Janus kinase inhibitor oclacitinib (A poquel®) in client-owned dogs with atopic dermatitis. Vet Dermatol (2013) 24(6):587–e142. doi: 10.1111/vde.12088

110. Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol (2019) 80(4):913–21.e9. doi: 10.1016/j.jaad.2018.11.028

111. Simpson E, Lacour JP, Spelman L, Galimberti R, Eichenfield L, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol (2020) 183(2):242–55. doi: 10.1111/bjd.18898

112. Szalus K, Trzecki M, Nowicki RJ. JAK-STAT inhibitors in atopic dermatitis from pathogenesis to clinical trials results. Microorganisms (2020) 8(11):1743. doi:10.3390/microorganisms8111743

113. Bissonnette R, Maari C, Forman S, Bhatia N, Lee M, Fowler J. The oral JAK/SYK inhibitor ASN002 demonstrates efficacy and improves associated systemic inflammation in patients with moderate-to-severe atopic dermatitis: results from a randomised, double-blind, placebo-controlled study. Br J Dermatol (2019) 181(4):733–42. doi: 10.1111/bjd.17932

114. Ross JA, Nagy ZS, Cheng H, Stepkowski SM, Kirken RA. Regulation of T cell homeostasis by JAKs and STATs. Arch Immunol Ther Exp (2007) 55(4):231–45. doi:10.1007/s00005-007-0030-x

115. Saraiva M, Christensen JR, Veldhoen M, Murphy TL, Murphy KM, O’Garra A. Interleukin-10 production by Th1 cells requires interleukin-12-induced STAT4 transcription factor and ERK MAP kinase activation by high antigen dose. Immunity (2009) 31(2):209–19. doi: 10.1016/j.immuni.2009.05.012

116. Mondoulet L, Dioszegy V, Puteaux E, Ligeois M, Dfbelt V, Plaquet C, et al. Specific epicutaneous immunotherapy prevents sensitization to new allergens in a murine model. J Allergy Clin Immunol (2015) 135(6):1546–57.e4. doi: 10.1016/j.jaci.2014.11.028