

ALLERGY

Pinning allergies on pathogenic T_H2 cells

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A new proinflammatory subtype of antigen-specific T_H2 cell that expresses CD161 emerges as the pathogenic cell type in allergic disease and is deleted during allergen-specific immunotherapy (Wambre *et al.*, this issue).

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Allergic diseases, including asthma, allergic rhinitis (hay fever), atopic dermatitis (eczema), food allergy, and anaphylaxis, are major health concerns with increasing prevalence particularly in the “developed” world. These diseases affect a large proportion of the population, result in considerable morbidity, and are, in some circumstances, life-threatening. Asthma affects about 300 million people worldwide and kills several thousand people each year in the United States alone. Anaphylaxis is frequently life-threatening, although the use of adrenaline/epinephrine auto-injectors has improved this situation in some countries. It has long been known that being atopic (allergic) and having one allergic disease increases the likelihood of developing other allergic diseases during a person’s lifetime—the so-called atopic march. Allergic diseases are driven by an inappropriate immune response to normally innocuous antigens such as cat dander, peanuts, grass pollen, or house dust mites. Despite intensive research, we still do not fully understand why some individuals develop antigen-specific pathogenic immune responses to these allergens. Almost as mysterious are the T cells that drive the allergic response. In this issue, Wambre *et al.* bring us a step closer to identifying and understanding the enigmatic T cells underpinning allergy (1). They show that a new subset of pathogenic T_H2 cells (T_H2A) is found specifically in patients with allergic disease and link depletion of T_H2A cells with allergen desensitization immunotherapy.

T_H2 CELLS IN ALLERGIC DISEASE

A number of elegant studies in both mouse and human have shown that the pathology of allergic disease is driven by the type 2 cytokines, which induce different hallmarks of allergic disease. The type 2 cytokine IL-4 induces B cell isotype switching to produce IgE; IL-5 promotes eosinophil differentiation, migration, and survival; and IL-13 induces mucus hypersecretion and fibrosis. Type 2 cytokines can be

produced by a variety of innate immune cell types, including mast cells, basophils, and the more recently identified group 2 innatelymphoid cells (ILC2s). However, antigen-specific expression of type 2 cytokines in response to allergen is restricted to the T_H2 subset of T helper cells.

The T_H2 cytokines are not constitutively expressed by T_H2 cells but are transiently activated and secreted upon antigen stimulation, making it challenging to identify the T_H2 cell subset in the absence of a specific allergen. In humans, T_H2 cells can be identified by expression of the prostaglandin D₂ receptor CRT_H2 (also known as DP2 or CD294). Paradoxically, however, numerous studies have failed to detect an increased prevalence of CRT_H2⁺ T_H2 cells in patients with allergic disease. Recent studies have suggested that there is functional heterogeneity within the T_H2 cell subset, with some memory T_H2 cell populations being able to express high levels of IL-5 (2, 3), IL-17 (4), or IFN-γ (5) alongside IL-4 and IL-13, giving rise to the concept of a pathogenic effector T_H2 (peT_H2 or T_{path}2) cell subset (6). The nature of this T_H2 cell subset and the methods used to identify it are an area of active research, with several potential phenotypic markers being proposed in both mouse and human studies. These markers include the receptors for the epithelial-derived cytokines IL-25 (IL17RB) (7), IL-33 (ST2) (8), and thymic stromal lymphopoietin (TSLP receptor; TSLPR) (9). These epithelial-derived cytokines are believed to be released from damaged epithelium in response to viral infection, allergen exposure, or physical damage and potentially induce type 2 cytokine production from a variety of cell types, including ILC2s, basophils, mast cells, and T_H2 cells.

IDENTIFICATION OF PATHOGENIC T_H2 CELLS

In their new study, Wambre *et al.* (1) identified allergen-specific T cells in patients by se-

lecting patients with allergy to alder tree pollen, using peptides from alder tree allergens in combination with fluorescently labeled major histocompatibility class II (MHCII) tetramers. This is how an allergen-specific T cell would normally “see” an allergen on the surface of an antigen-presenting cell and therefore allowed the investigators to accurately identify the T cells responsible for the response to a particular allergen. They used this approach to screen a large panel of cell surface molecules in an attempt to identify markers that are selectively expressed on allergen-specific T helper cells. As expected, they found that most allergen-specific T cells were CRT_H2⁺ and had a memory phenotype (CCR7^{low}CD27^{low}CD45RB^{low}). Crucially, however, they also identified two surface markers that were selectively up-regulated in the allergen-specific T_H2 cell population: CD161 and CD49d. The expression of the C-type lectin receptor CD161 is closely associated with inflammatory T_H17 cells; however, the authors convincingly demonstrate that these CD27[−]CD45RB[−]CRT_H2⁺CD161⁺ T_H2 cells do not express hallmarks of T_H17 differentiation, including IL-17 and RORγt, distinguishing these cells from those observed by Cosmi *et al.* (4). They went on to show that in patients with a wide range of allergies, including food (peanut), perennial (cat), seasonal pollen (Timothy grass), and mold (*Aspergillus*), antigen-specific T_H2 cells with the CD27[−]CD45RB[−]CRT_H2⁺CD161⁺CD49d⁺ phenotype were present in greater numbers, whereas they were absent in nonallergic people, suggesting that these cells may be causing allergic disease.

Although identifying allergen-specific T_H2 cells that may cause disease is a big step forward, the authors’ approach requires prior knowledge of the allergen involved and the ability to develop specific peptide MHCII tetramers against the allergen. From a clinical viewpoint, this may not always be possible and would thus restrict the usefulness of this approach. However, Wambre and colleagues went on to see whether they could identify this T_H2 cell population in patients without using the MHCII tetramer technology. They found that,

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compared with nonallergic people, allergic individuals had higher frequencies of these pathogenic T_H2 cells, dubbed “ T_H2A cells” and defined as $CD27^-CD45RB^+CRT_{H2}^+CD161^+CD49d^+$ (Fig. 1).

To attempt to demonstrate that the pathogenic T_H2 cells were the cells that respond to allergen in atopic individuals, the researchers examined patients undergoing two different allergen challenge situations: natural exposure of hay fever sufferers during the pollen season and a double-blind, placebo-controlled peanut challenge in patients with peanut allergy. In both situations, the pathogenic T_H2 cell subset ($CD27^-CRT_{H2}^+CD161^+$) was activated in response to in vivo allergen challenge, as assessed by expression of the activation marker CD38, in contrast to the conventional T_H2 cell population ($CRT_{H2}^+CD161^-$). Thus, the authors appear to have identified the allergen-responsive

pathogenic T_H2 cell population in humans and report that it is a subset of the total T_H2 cell pool.

Allergen desensitization immunotherapy is a mainstay of treatment for several allergic diseases, including allergic rhinitis and bee venom anaphylaxis, although the precise mechanisms of action are not fully understood. Patients are administered either subcutaneously or sublingually increasing amounts of allergen to desensitize them. Wambre *et al.* went on to examine the impact of a peanut immunotherapy treatment on their pathogenic T_H2 cell subset (1). Remarkably, they found that the pathogenic T_H2 cell population was selectively deleted in patients undergoing the active immunotherapy treatment and that this specifically correlated with clinical benefit, suggesting that pathogenic T_H2 cells are a clinically relevant target cell population in allergic disease.

MECHANISTIC INSIGHTS

To explore the mechanisms by which pathogenic T_H2 cells might cause disease, the investigators performed multiparametric intracellular cytokine staining and demonstrated that pathogenic T_H2 cells express more IL-5 and IL-9 than do conventional T_H2 cells and do not express IL-17 or IFN- γ . Transcriptome profiling of the pathogenic T_H2 cells identified an interesting set of genes up-regulated in this population, including the IL-25 receptor (*IL17RB*), IL-33 receptor (ST2; *IL1RL1*) and TSLPR (*CRLF2*), Cox-2 (*PTGS2*), and hematopoietic prostaglandin D synthase (*HPGDS*). Collectively, this gene expression profile appears very similar to those of the various pathogenic effector T_H2 cell populations identified by several other groups. We have previously identified $IL17RB^+ST2^+$ T_H2 cells in nasal polyposis (7), and others have found $HPGDS^+$ pathogenic effector T_H2 cells in patients with eosinophilic gastrointestinal disease and atopic dermatitis (9). Wambre *et al.* failed to detect surface expression of IL17RB or ST2 in their experiments, possibly due to the use of different antibodies for immunostaining (1). It is highly likely that all of these studies have been examining the same or very similar pathogenic effector T_H2 cell subsets, which provides hope that therapies targeting this cell population will provide benefit in a wide variety of allergic diseases.

One outstanding question regarding pathogenic T_H2 cells surrounds the mechanism of differentiation compared to conventional T_H2 cells. Classical T_H2 and pathogenic T_H2 cells express GATA3, the master regulator of T_H2 differentiation. It will be important to determine whether additional transcription factors are involved in directing the pathogenic T_H2 transcriptional program; one candidate for this could be the nuclear receptor PPAR γ , reported to be up-regulated in pathogenic T_H2 cells by Wambre *et al.* (1). It will also be important to understand the role of the epithelial-derived cytokines in regulating pathogenic T_H2 cell function and activation.

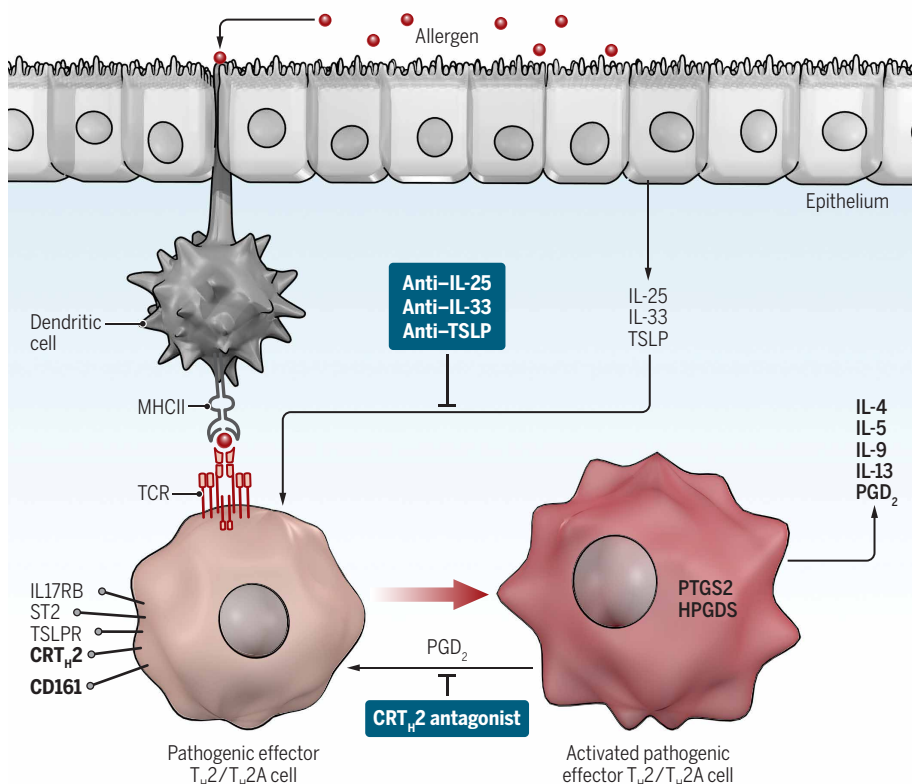


Fig. 1. Pathogenic effector T_H2 cells in the spotlight. Allergen challenge to the epithelium allows dendritic cells (gray) to present allergen (red circles) to pathogenic effector T_H2 cells/ T_H2A cells and induces release of epithelial-derived cytokines such as IL-25, IL-33, and TSLP. Pathogenic effector T_H2 cells (pink) are allergen-specific $CD4^+$ T cells identified by a panel of cell surface markers ($CD27^-CD45RB^+CRT_{H2}^+CD161^+CD49d^+$) and epithelial cytokine receptors (IL17RB, ST2, and TSLPR). Pathogenic effector T_H2 cells are activated by allergen and produce type 2 cytokines such as IL-4, IL-5, IL-9, and IL-13. These cells can also secrete prostaglandin D_2 (PGD_2) in response to epithelial cytokines due to their expression of *PTGS2* and *HPGDS*. CRT_{H2} antagonists and antibodies targeting epithelial cytokines may block pathogenic effector T_H2 cell recruitment or activation, thus ameliorating the allergic response. These pathogenic effector T_H2 cells that drive allergen-specific immune responses may be a useful therapeutic target for treating allergic disease.

CLINICAL IMPLICATIONS

The identification of pathogenic T_H2 cells as a clinically important cell type in allergic disease will enable researchers to use the panel of cell surface markers reported by Wambre *et al.* (1) to study the pathogenic T_H2 response to new treatments for these various diseases. The study by Wambre *et al.* is timely

because several pharmaceutical companies have developed new therapeutics targeting IL-25, IL-33, TSLP, and their respective receptors (IL17RB, ST2, and TSLPR), and these therapeutics are now entering clinical testing. Furthermore, given that pathogenic T_H2 cells express both the biosynthetic pathway for PGD₂ production (Cox-2 and HPGDS) and a receptor for PGD₂ (CRT_{H2}), it will be critical to examine the effect of blockade of this pathway in allergic disease. The recent study of the drug fexipiprant in asthma, a small-molecule antagonist of CRT_{H2}, suggests that CRT_{H2} antagonism may be one mechanism worth exploring for treatment of other allergic diseases (10). The study by Wambre *et al.* implicates a new pathogenic T_H2 cell subset in allergic disease and reveals a panel of cell surface markers that the research community now can use to examine the importance of these pathogenic T_H2 cells in clinical trials of new therapeutic agents.

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