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. Although mysterious are the T cells that drive the allergic response. In this issue, Wambre et al bring us a mysterious are the T cells that drive the allergic response. In this issue, Wambre et al bring us a mysterious are the T cells that drive the allergic response. In this issue, Wambre et al bring us a...
compared with nonallergic people, allergic individuals had higher frequencies of these pathogenic Th2 cells, dubbed "Th2A cells" and defined as CD27−CD45RB−CRT2+CD161+CD49d+ (Fig. 1).

To attempt to demonstrate that the pathogenic Th2 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 Th2 cell subset (CD27−CD45RB−CD161+CD161−) was activated in response to in vivo allergen challenge, as assessed by expression of the activation marker CD38, in contrast to the conventional Th2 cell population (CRT2+CD161+). Thus, the authors appear to have identified the allergen-responsive pathogenic Th2 cell population in humans and report that it is a subset of the total Th2 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 Th2 cell subset (1). Remarkably, they found that the pathogenic Th2 cell population was selectively deleted in patients undergoing the active immunotherapy treatment and that this specifically correlated with clinical benefit, suggesting that pathogenic Th2 cells are a clinically relevant target cell population in allergic disease.

**MECHANISTIC INSIGHTS**

To explore the mechanisms by which pathogenic Th2 cells might cause disease, the investigators performed multiparametric intracellular cytokine staining and demonstrated that pathogenic Th2 cells express more IL-5 and IL-9 than do conventional Th2 cells and do not express IL-17 or IFN-γ. Transcripome profiling of the pathogenic Th2 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 Th2 cell populations identified by several other groups. We have previously identified IL17RB–ST2+ Th2 cells in nasal polyposis (7), and others have found HPGDS+ pathogenic effector Th2 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 Th2 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 Th2 cells surrounds the mechanism of differentiation compared to conventional Th2 cells. Classical Th2 and pathogenic Th2 cells express GATA3, the master regulator of Th2 differentiation. It will be important to determine whether additional transcription factors are involved in directing the pathogenic Th2 transcriptional program; one candidate for this could be the nuclear receptor PPARγ, reported to be up-regulated in pathogenic Th2 cells by Wambre et al. (1). It will also be important to understand the role of the epithelial-derived cytokines in regulating pathogenic Th2 cell function and activation.

**CLINICAL IMPLICATIONS**

The identification of pathogenic Th2 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 Th2 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\textsubscript{H}2 cells express both the biosynthetic pathway for PGD\textsubscript{2} production (Cox-2 and HPGDS) and a receptor for PGD\textsubscript{2} (CRT\textsubscript{H}2), it will be critical to examine the effect of blockade of this pathway in allergic disease. The recent study of the drug fevipiprant in inhibition of activity of the transcription factor GATA3. 

The importance of these pathogenic TH\textsubscript{2} cells reveals a panel of cell surface markers that the TH\textsubscript{2} cell subset in allergic disease and reprogramming to generate a stable GATA-3+T-bet+ cell signature in nasal mucosa. J. Allergy Clin. Immunol. 137, 1514–1524 (2016).

The study by Wambre et al. implicates a new pathogenic T\textsubscript{H}2 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\textsubscript{H}2 cells in clinical trials of new therapeutic agents.

REFERENCES AND NOTES


Acknowledgments: D.J.C. received research grant funding from Asthma UK, Medical Research Council, Biotechnology and Biological Sciences Research Council, GlaxoSmithKline, MedImmune, Midlands Asthma and Allergy Research Association, and the National Institute for Health Research Leicester Biomedical Research Centre.

10.1126/scitranslmed.aao0392

Citation: D. J. Cousins, Pinning allergies on pathogenic T\textsubscript{H}2 cells. Sci. Transl. Med. 9, eaao0392 (2017).
Pinning allergies on pathogenic T_{H2} cells

David J. Cousins

Sci Transl Med 9, eaao0392.
DOI: 10.1126/scitranslmed.aao0392