Commentary

Snapshots of CD4$^+$ T cell plasticity in the pathogenesis of allergic asthma

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Submitted Jun 26, 2016. Accepted for publication Jul 02, 2016.
doi: 10.21037/jtd.2016.08.19
View this article at: http://dx.doi.org/10.21037/jtd.2016.08.19

Allergic asthma is one of the well-known type 2 inflammatory diseases and is mainly mediated by T helper type 2 (Th2) cells (1). Environmental allergens such as house dust mite (HDM) causes lung eosinophilia (2). Followed by activation of lung epithelial cells and subsequent release of alarmins such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 (3,4), dendritic cells (DCs) and B cells participate to prime naïve CD4 T cells to differentiate them into Th2 effector cells to secrete Th2 cytokines (IL-4, IL-5 and IL-13) and to produce B cell-mediated humoral immune responses by Ig (immunoglobulin)-E (5,6). Recently platelets were shown to participate in HDM-induced asthma stimulating Th2 cell differentiation (7). IL-5 primarily induces eosinophil migration, recruitment and activation (8) while IL-13 induces airway remodeling and airway hyperreactivity (9). IL-4 is produced by CD4 T cells, basophils, and innate lymphoid type 2 cells (ILC2s) (10). While the contribution of effector Th2 cells to the asthma pathology has been extensively studied, it remained unanswered whether T cell plasticity in asthma plays an important role. T cell plasticity has been considered as one of the key factors in T cell-mediated immune responses particularly in pathogenic microenvironments (11).

Recently, Ballesteros-Tato *et al.* showed that follicular helper T cells (Tfh cells) expressing IL-4 are induced by HDM sensitization and these cells become fully committed Th2 cells (12). This is a solid, thorough, and well-designed study to elucidate the process of Tfh generation following HDM challenge with various mouse model systems with cytokine reporter mice, and it also addressed the important question of CD4$^+$ T cell plasticity in the HDM-induced asthma model. Since B cell-mediated IgE responses are present in the HDM-induced allergic asthma model, one of the main questions in the model is whether an intermediate stage of CD4$^+$ T cell differentiation after an initial challenge of HDM might occur. The primary results suggest that Tfh cells, but not Th2 cells, are formed by the initial HDM challenge and these Tfh cells are precursors of effector Th2 cells for asthma development. The study also showed that both B cells and DCs are required for Tfh cell generation upon priming, and that depletion of Tfh generation subsequently failed to generate effector Th2 cells.

Experimentally, Ballesteros-Tato *et al.* demonstrated that B cells are critical to form Th2 cell responses using B cell-deficient μMT mice and IL-4 reporter (4Get) mice using a 20-day HDM-induced asthma model. Briefly, HDM was administered intranasally from day 1 to 4, and then day 15 to day 18 for the rechallenge phase. A surprising finding is that the homogeneity of IL-4$^+$CD4$^+$ T cells in the medLN that become Tfh cells after the initial HDM challenge. Although it has been thought that Tfh cells can produce IL-4 (13), practically all the GFP$^+$(IL-4$^+$) CD4$^+$ T cells in the medLN expressed the archetypal Tfh cell markers (e.g., CXCR5, PD-1, Bcl-6, ICOS, and GL7), indicating that IL-4-committed Tfh cell generation is a critical step to produce functional Th2 effector T cells in their experimental model. The GFP$^+$ CD4$^+$ T cells also expressed IL-21 and IL-4, but very little IL-2, IL-5 and IL-13, suggesting that they are functionally IL-4-committed Tfh cells, not Th2 effector T cells. This exclusive generation of Tfh cells after the initial challenge of HDM was further tested by depleting pre-existing IL-4-committed Tfh using a commercial BCL-6 inhibitor 79-6 (14). These results shift the traditional paradigm of Th2 cell differentiation in the allergic asthma model to a "two-step

differentiation" model through IL-4-committed Tfh cells.

Other important questions in the HDM-induced allergic asthma model are (I) how, where and when HDM-derived antigens are presented and (II) whether B cells and DCs are both required to orchestrate IL-4-committed Tfh cell generation. Ballesteros-Tato *et al.* answered these questions with the genetic ablation of B cells or $CD11c^+$ DCs using μMT or CD11c DTR (diphteria toxin receptor) mice. They also analyzed the anatomical localization of HDM antigens with fluorescently labeled HDM *in vivo*. Interestingly, this fluorescently labeled HDM was primarily found in the interfollicular area, co-localized with the area in which $CD11c^+$ cells reside. Alexa 647-labeled HDM was located in B cell follicles 72 hours after HDM administration, providing anatomical evidence that the orchestration of B cells and DCs is instrumental for IL-4-committed Tfh cell generation. Together with data using μMT mice and CD11c-DTR mice, these data demonstrated three important points: (I) lung-migratory $CD11c^+$ DCs bear HDM; (II) HDM-derived antigen(s) preferentially localize within the periphery of the B cell follicles early after HDM sensitization and (III) HDM-derived antigen is subsequently transferred to cells in the follicle.

Regarding the question of the fate of IL-4-committed Tfh cells, Ballesteros-Tato *et al.* demonstrated that Tfh cells in the medLN migrate to the lung after HDM rechallenge. To track the fate of IL-4-committed Tfh cells that were generated by HDM the authors used HDM-OVA after adoptive transfer of IL-4-committed Tfh cells. $IL\text{-}21^+IL\text{-}2^-$ Tfh cells were significantly expanded after HDM rechallenge and the progeny cells rapidly accumulated in the lung differentiated into IL-4 and IL-13 double-producing effector Th2 cells. Importantly, these Th2 effector cells no longer produced IL-21 or other Tfh cell markers, suggesting that the recall response permanently and irreversibly changes $CD4^+$ T cell fate from IL-4-committed Tfh cells into Th2 cells.

The study provides new insight on the initial steps of $CD4^+$ T cell differentiation following exposure to HDM allergen. The results explain why the initial exposure to allergen would not cause pulmonary pathology yet it will leave a cellular mark. The recurrent allergen challenges generate IL-4-committed Tfh cells in the medLN under the orchestration of B cells and DCs and it is a critical step for effector Th2 cell generation. It would be worthwhile to track the antigen specificity of IL-4-committed Tfh cells since now Derp1 specific MHC II tetramer is available (15). For example, now it is possible to test whether Tfh cells become Derp1 antigen-specific memory Tfh cells. If IL-4-committed Tfh cells have a long-lived antigen-specific memory $CD4^+$ T cell phenotype, it would be an important starting point for developing a new intervention that targets the inhibition of Th2 cell differentiation in allergic asthma.

An important point for future studies is whether these results are HDM allergen specific. At this time, most allergic asthma reactions have Th2 responses with humoral immune responses, and thus this new study provides very novel insight. However, further rigorous studies to test other allergens (e.g., chitin or cockroach) to test whether similar results can be obtained. It should be noted that IL-4 is driving eosinophil migration, but also it has been shown that other subsets such as ILC2s may contribute to IL-4-committed Tfh cell generation or subsequent irreversible effector Th2 cell commitment. Furthermore, it has not been tested whether neutrophilic or severe asthma is affected by this model, thus further studies are warranted.

Clinically, it would be worth pursuing whether IL-4-committed Tfh cells in the peripheral blood are present to predict the prevalence of asthma development. Seasonal allergic asthma would be an ideal target to study since the exposure and re-exposure will have predictable outcomes. On the other hand, it might be challenging to detect IL-4-committed Tfh cells in the fully developed asthma patients since the differentiation of IL-4-committed Tfh cells to Th2 effector cells is irreversible.

Acknowledgements

Funding: This work was supported by the National Institutes of Health (R01 CA168670 to A.B.).

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Ai Ge (Nanjing Medical University, Nanjing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Ballesteros-Tato A, Randall TD, Lund FE, *et al.* T Follicular Helper Cell Plasticity Shapes Pathogenic T Helper 2 Cell-Mediated Immunity to Inhaled House Dust Mite. Immunity 2016;44:259-73.

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Cite this article as: Chae WJ, Bothwell AL. Snapshots of CD4+ T cell plasticity in the pathogenesis of allergic asthma. J Thorac Dis 2016;8(9):E1010-E1012. doi: 10.21037/jtd.2016.08.19