TISSUE-RESIDENT T CELLS

The highs and lows of CD4+ tissue-resident T cells in lung fibrosis

Chronic exposure to fungal antigen drives the development of two subsets of CD4+ T_{RM} cells, distinguished by high or low expression of the integrin CD103, with opposing roles in inflammation-induced lung fibrosis.

Maximilien Evrard and Laura K. Mackay

Tissue-resident memory T cells (T_{RM} cells) are a subset of T cells that are critically involved in the immunosurveillance of peripheral tissues during infection and cancer[1]. Although substantial effort has defined the properties of CD8+ T_{RM} cells, the understanding of CD4+ T_{RM} cells is comparatively limited. In this issue of *Nature Immunology*, Ichikawa et al. identify two distinct subsets of lung-resident CD4+ T cells during chronic inflammation: a pathogenic CD103^{lo} population that promotes tissue fibrosis, and a protective CD103^{hi} regulatory T cell (T_{reg} cell) subset that keeps this process in check[2].

Memory T cells can be divided into two categories by virtue of their tissue trafficking and functional properties. Circulating memory T cells survey the blood and lymphoid organs, whereas T_{RM} cells are strategically positioned within peripheral tissues, where they provide local immune protection after reinfection. Akin to their CD8+ counterparts, CD4+ T_{RM} cells have been suggested to be beneficial in the context of infection, during which they can secrete cytokines such as IFN-γ that facilitate viral clearance after re-exposure to the pathogen[1]. On the other hand, studies have also linked CD4+ T_{RM} cells to pathological autoimmune responses during colitis and asthma[3,4]. Thus, in the context of disease, CD4+ T_{RM} cells probably play either helpful roles or deleterious roles, although what contributes to these opposing contributions has not been defined until now.

To assess CD4+ T cell responses, Ichikawa et al. repeatedly exposed mice to antigens derived from *Aspergillus fumigatus*[2], a fungus associated with severe persistent asthma. Chronic stimulation with *Aspergillus* antigen results in inflammation-induced lung fibrosis, accompanied by an increase in effector cytokines and infiltration of immune cells around the bronchi. One key observation in this chronic-antigen-stimulation model is substantial infiltration into the lung parenchyma of CD4+ T cells with variable expression of the surface molecules CD69 and CD103, two markers that have been associated with tissue residency. RNA sequencing of the various CD4+ T cell populations in the inflamed lungs shows that CD69+CD103^{lo} and CD69+CD103^{hi} CD4+ T cells downregulate genes encoding molecules involved in tissue egress (*S1pr1*, *Klf2* and *Ccr7*) and upregulate *Cxcr6* (which encodes the chemokine receptor CXCR6), consistent with a tissue-resident phenotype. Furthermore, both CD103^{lo} cells and CD103^{hi} cells show increased expression of genes encoding fibrosis-related molecules, suggestive of a more predominant role for these two populations in lung inflammation than that of their circulating CD4+ T cell counterparts. Classic parabiosis experiments show that CD4+ T cells in the lungs of *Aspergillus* antigen–exposed mice do not equilibrate via the blood, which confirms that these cells are indeed a long-term resident population.

Notably, the authors observe that the CD103^{lo} and CD103^{hi} tissue-resident populations in the lung are functionally distinct. The production of effector cytokines, including IL-4, IL-5, IL-13 and IL-17A, is restricted mostly to the CD103^{lo} subset, which is associated with the pathology of fibrotic responses in the lungs. The CD103^{hi} population expresses genes, including *Foxp3*, *Klrg1* and *Prdm1* (which encodes the transcription factor Blimp-1), that are characteristic of T_{reg} cells. Strikingly, antibody-mediated depletion of the CD103^{hi} tissue-resident T_{reg} cell population is shown to significantly aggravate fibrosis (Fig. 1). Together these data provide evidence of functional diversity between different tissue-resident CD4+ T_{RM} cells in the lungs during chronic inflammation-induced fibrosis. This includes T cell populations that act in an opposing manner, with the CD103^{lo} population acting as a driver of disease and the CD103^{hi} population forming a classical anti-inflammatory regulatory subset that dampens the inflammatory response.

What remains undefined are the mechanisms that select between functionally distinct CD4+ T cell populations in this model of disease. It is known that the fibrosis-associated cytokine TGF-β can induce expression of the transcription factor FoxP3 by CD4+ T_{reg} cells as well as that of CD103, which is the identifying feature of this population. Therefore, one could speculate that fibrosis might contribute to the generation of T_{reg} cells in a TGF-β-dependent manner to drive a negative feedback loop that limits tissue damage elicited by other immune cell populations within the lungs. Regardless, the findings of this study clearly link T_{RM} cells to tissue pathology, with distinct subsets contributing to the amelioration or aggravation of disease. Several strategies could be implemented to remove pathogenic T_{RM} cells from tissues. Although CD8+ T_{RM} cells are generally found in association with epithelial cells, CD4+ T_{RM} cells are often found in clusters with other immune cells. CD4+ T_{RM} cells can be retained in these aggregates via production of CCL5, with blockade of this chemokine sufficient to disrupt clusters of immune cells, which results in the loss of CD4+ T_{RM} cells[5,6]. In the lungs, inflammation caused by infection or an allergic reaction drives the generation of ectopic lymphoid structures called 'inducible bronchus-associated lymphoid tissues'. The authors of the present study[2] previously found, in a model of allergic asthma, that pathogenic cells of the T_H2 subset of helper T cells are maintained within those structures and that disruption of the structures leads to the disappearance of these cells[7]. Nonetheless, disruption of clusters of immune cells could represent a promising method for the removal of pathogenic CD4+ T_{RM} cells from tissues. Another approach is to target factors necessary for the maintenance of T_{RM} cells, such as the local blockade of cytokines, including IL-2 or IL-7, shown to be required for the development of lung CD4+ T_{RM} cells in various settings[4,7,8]. When placed in the

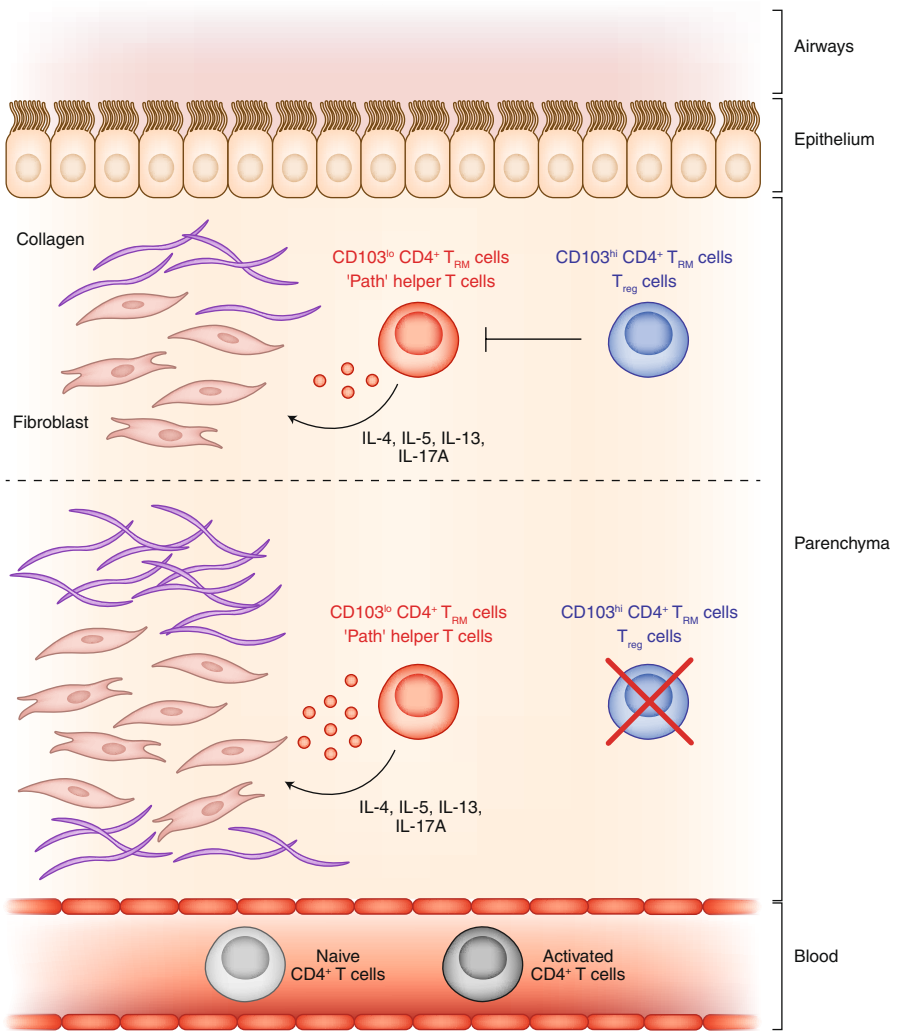

Fig. 1 | CD103^{hi} tissue-resident T_{reg} cells control fibrotic responses elicited by CD103^{lo} pathogenic CD4$^+$ T_{RM} cells in the lungs. Chronic exposure to *A. fumigatus* antigen promotes the development of two types of CD4$^+$ T_{RM} cells in the lung parenchyma. Pathological CD69$^+$CD103^{lo} CD4$^+$ T_{RM} cells ('Path' helper T cells) secrete pro-inflammatory cytokines (IL-4, IL-5, IL-13 and IL-17A) that drive tissue fibrosis and deposition of collagen around the bronchi. CD69$^+$CD103^{hi} tissue-resident T_{reg} cells limit tissue pathology. Depletion of CD103^{hi} tissue-resident T_{reg} cells exacerbates inflammation-induced lung fibrosis.

context of this current study, blockade of IL-7 might be a possible way to eliminate pathogenic CD4$^+$ T_{RM} cells without targeting resident T_{reg} cells with low expression of its receptor, IL-7R.

A growing body of evidence suggests that the development of memory T cells is influenced by a multitude of factors, including cellular origin (CD4$^+$ T cells versus CD8$^+$ T cells), migratory properties (circulating cells versus tissue-resident cells) and exposure to factors within the tissue microenvironment. In addition to those levels of regulation, priming conditions may add another layer of complexity that results in the differentiation into distinct lineages (T_H1 cells, T_H2 cells, T_H17 cells and T_{reg} cells, in the case of CD4$^+$ T cells). For example, a study has demonstrated the co-existence of two types of skin CD8$^+$ T_{RM} cells that produce either IFN-γ or IL-17A; the cells were primed by different dendritic cells subsets following association with the commensal *Staphylococcus epidermidis*[9]. This indicates that T cell interactions that precede the formation of T_{RM} cells may also play a part in shaping the establishment of functional diversity within tissues.

Collectively, the work by Ichikawa et al. demonstrates that distinct CD4$^+$ T_{RM} cell subsets with fundamentally opposing roles can co-exist within the same tissue[2]. Future studies will be needed to establish the defining features of different tissue-resident populations and to elucidate the mechanisms that drive functional heterogeneity during health and disease. ❐

Maximilien Evrard and Laura K. Mackay*

Department of Microbiology and Immunology, The University of Melbourne, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia.

**e-mail: lkmackay@unimelb.edu.au*

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Competing interests

The authors declare no competing interests.