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Immunity

Interleukin-2-Dependent Allergen-Specific Tissue-Resident Memory Cells Drive Asthma

Highlights

- Allergen-specific $CD4^+$ Th2 memory cells were tracked with MHC class II tetramers
- Lung resident memory T cells formed after intranasal house dust mite antigen exposure
- IL-2 signaling was required for the formation of lung-resident memory Th2 cells
- The lack of BCL-6 expression or B cells promoted T cell entry into the lung

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In Brief

The contribution of allergen-specific Th2 memory cells to airway inflammation is not clear. Pepper and colleagues track the development and function of endogenous house dust mite antigen-specific $CD4^+$ T cells and find that pathogenic lung Th2 cells are tissue resident memory cells that depend on IL-2 signaling for their generation.

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Interleukin-2-Dependent Allergen-Specific Tissue-Resident Memory Cells Drive Asthma

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SUMMARY

Exposure to inhaled allergens generates T helper 2 (Th2) CD4$^+$ T cells that contribute to episodes of inflammation associated with asthma. Little is known about allergen-specific Th2 memory cells and their contribution to airway inflammation. We generated reagents to understand how endogenous CD4$^+$ T cells specific for a house dust mite (HDM) allergen form and function. After allergen exposure, HDM-specific memory cells persisted as central memory cells in the lymphoid organs and tissue-resident memory cells in the lung. Experimental blockade of lymphocyte migration demonstrated that lung-resident cells were sufficient to induce airway hyper-responsiveness, which depended upon CD4$^+$ T cells. Investigation into the differentiation of pathogenic Trm cells revealed that interleukin-2 (IL-2) signaling was required for residency and directed a program of tissue homing migrational cues. These studies thus identify IL-2-dependent resident Th2 memory cells as drivers of lung allergic responses.

INTRODUCTION

Atopic asthma affects between 50%–80% of asthmatics and begins when children are exposed to common aeroallergens including pollen, animal dander, fungal spores, or house dust mites (HDM) (Locksley, 2010). The majority of atopic asthma cases are characterized by T helper 2 (Th2) cell-associated cellular processes (Wenzel, 2012). During the sensitization phase, allergen-specific CD4$^+$ Th2 cells expand, acquire the capacity to express "type 2" cytokines, and upregulate chemokine receptors and integrins associated with migration to various anatomical sites. The type 2 cytokines (interleukin-4 [IL-4], IL-5, and IL-13) orchestrate multiple events associated with asthma including eosinophil maturation and survival, airway hyper-responsiveness, and B cell isotype switching to immunoglobulin E (IgE) (Holgate, 2012). After this period of expansion and differentiation, there is a protracted contraction phase in which approximately 90% of the expanded population dies and a small population of differentiated memory cells is retained (Pepper et al., 2010). In both murine models of disease and in asthmatic patients, CD4$^+$ memory T cells are thought to be involved in recurrent episodes of inflammation (Lanzavecchia et al., 1983; Mojtabavi et al., 2002). Due to the difficulty in tracking small populations of CD4$^+$ Th2 cells that express allergen-specific TCRs, little is known about endogenous Th2 memory cell differentiation, maintenance, or homing properties.

In humans and mice, there are circulating and non-circulating CD8$^+$ and CD4$^+$ memory T cells. Circulating memory T cells exist in two subsets: central memory (Tcm) and effector memory (Tem) T cells (Sallusto et al., 1999). Tcm cells express the chemokine receptor CCR7 and L-selectin, which direct recirculation through lymphoid tissues. CCR7$^-$ Tem cells express receptors needed for migration into nonlymphoid tissues and when stimulated with their relevant peptide-MHCII (pMHCII) ligand, rapidly produce cytokines. In models of Th1 memory, differentiation of CXCR5$^-$ Teff and Tem is promoted by signaling through the cytokine IL-2, while differentiation of the CXCR5$^+$ T follicular helper cells (Tfh) and Tcm cells depends upon expression of the transcription factor BCL6 (Choi et al., 2011; Pepper et al., 2011). It is not known whether these same mechanisms are involved in Th2 memory formation.

A third population of memory T cells has also been described that are non-circulating and are retained in the tissues, called tissue-resident memory (Trm) cells (Mueller et al., 2013). Studies primarily examining CD8$^+$ T cells have defined unique roles for Trm cells including the direct immediate control of local infection and the indirect modification of the tissue microenvironment to promote inflammation (Schenkel and Masopust, 2014). Although recent studies have begun to unravel the function of CD4$^+$ Trm cells in infection, less is known about how these cells contribute to immune pathology because antigen-specific memory cells that reside in nonlymphoid tissues are rare (Gebhardt et al., 2011; Glennie et al., 2015; Sakai et al., 2014; Shin and Iwasaki, 2012; Teijaro et al., 2011; Turner et al., 2014). Recent studies have overcome these issues by combining advances in MHC class II tetramer generation with novel intravascular (i.v.) staining procedures, magnetic bead

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