CHEST

Dendritic Cells in Human Lung Disease
Recent Advances

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Dendritic cells (DCs) are potent antigen-presenting cells. Because of their particular ability to initiate and regulate cell mediated and humoral immune responses, there is considerable interest in the role that DCs play in the pathogenesis of various lung diseases, especially those in which there is an excessive immune response to specific antigens (as in asthma) or a deficient immune response (as in lung cancer). A number of DC subpopulations have been defined in the lungs, including myeloid or conventional DCs that initiate T-cell immunity and antibody production and plasmacytoid DCs that have an important role in antiviral immunity and immune tolerance. Although an extensive body of literature has documented the role that DCs play in experimental models of lung disease, this review will highlight recent advances in our understanding of DC function in human disease, including asthma, COPD, antimicrobial immunity, and lung cancer. The future is likely to see new approaches whereby antigens and small molecules are targeted to receptors on particular DC subpopulations in order to modify pulmonary immune responses.

CHEST 2017; 151(3):668-673

KEY WORDS: dendritic cells; immune regulation

Dendritic cells (DCs) are potent antigen-presenting cells with key roles in the initiation and regulation of immune responses.[1-3] In the respiratory tract, they constantly sample inhaled antigens from the airway and alveolar epithelial surfaces, before migrating to regional lymph nodes where they present processed peptides to antigen-specific T cells. DC are unique in their capacity to activate naïve T cells and initiate primary immune responses in lymph nodes, and also play a central role in reactivating memory T-cell responses in the lungs. However, DC are far more than a passive conduit for delivering antigens to lymph node T cells. They are exquisitely sensitive to environmental signals be they derived from microbes, allergens, pollutants, or the products of tissue damage. DCs are responsive to pathogen-associated molecular patterns and damage-associated molecular patterns, and this markedly alters the signals they provide to T cells. Similarly, airborne pollutants such as diesel exhaust particles can alter DC function directly,[4] or via interactions with airway epithelial cells.[5] DC-derived signals regulate both the degree of T-cell activation and the nature or flavor of

ABBREVIATIONS: CD = cluster of differentiation; cDC = conventional dendritic cell; DC = dendritic cell; IFN = interferon; mDC = myeloid dendritic cell; pDC = plasmacytoid dendritic cell; Th = T helper cell; TSLP = thymic stromal lymphopoietin

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FUNDING/SUPPORT: J. W. U. is supported by grants from the National Health and Medical Research Council of Australia.

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DOI: http://dx.doi.org/10.1016/j.chest.2016.09.030

the immune response (eg, T helper (Th) 1, Th2, Th17, B-cell help) or immune regulation (Fig 1). DCs can therefore be viewed as finely tuned mechanisms for integrating and transferring information from the lung to regional lymph nodes. In health, the ensuing immune response is appropriate to the type of pathogen and the presence or absence of tissue damage; however, this is often perturbed in various lung diseases.

DC Subpopulations

Several DC subpopulations have been defined,[2,3] a fact that often seems bewildering to the nonexpert, especially when the markers used to define DCs differ between humans and mice. DCs are broadly divided into myeloid dendritic cells (mDCs), usually now referred to as conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs). Within the respiratory tract, cDCs form dense networks throughout the epithelium of large conducting airways, bronchioles, alveoli, and interstitial space. Detailed analyzes of murine lungs have revealed that at least two cDC subsets are present in steady state; these differ in function and anatomic location as reviewed previously by others.[2,3] The first subset of cDCs express the integrin cluster of differentiation (CD) 103, but they lack CD11b and are intimately associated with the respiratory epithelium where they project their dendrites between epithelial cells, allowing them to directly sample airway luminal contents. CD103+ DCs are dependent on the transcription factor interferon (IFN) regulatory factor 8 for their development, and are adept at taking up dead or damaged cells and presenting viral antigens to CD8 T cells.[2,3] The equivalent cDC subset in human lungs expresses CD141 and the C-type lectin domain family 9 member A. The second subset of lung cDCs are identified in mice by CD11b expression and in humans by CD1c: these are located beneath the basement membrane of the conducting airways and are dependent on the transcription factor IFN regulatory factor 4 for their development. There is good evidence that CD103+ DCs are biased toward induction of Th1 responses, whereas CD11b DCs preferentially induce Th2 or Th17 responses; however, this may vary according to the experimental model and type of antigen.[2,3] In the setting of inflammation and injury, a third subset of monocyte-derived DCs are rapidly recruited to the lungs. A recently published study used an elegant technique to distinguish tissue resident DCs in human lungs from DCs present in the vascular lumen.[6] The authors were able to define multiple myeloid subsets in lungs and draining lymph nodes, including pulmonary DCs coexpressing CD1a and CD1c and a variety of monocyte-derived subpopulations, including CD141+ DCs.[6]

pDCs are best characterized by their ability to synthesize prolific amounts of IFN in response to virus infections.[7] It is estimated that pDCs dedicate as much as 60% of their transcriptome to type I IFN production[8] and can release 100-fold more IFNα than any other known cell type.[9] Even though pDCs appear to be fully developed when they exit the bone marrow, they are relatively inefficient at presenting antigens to T cells and seem to play an important role in tolerance induction,[10] probably via induction of regulatory T cells.[11] In mice, pDC depletion induces a Th2 response and immunopathology after respiratory syncytial virus infection,[12] whereas our own studies have shown that pDCs from healthy people inhibit Th2 responses induced by rhinoviruses.[13] This regulatory mechanism may be lost in asthma. In humans, pDCs are identified by surface markers such as CD303 (a C-type lectin), CD304 or neuropilin-1, Ig-like transcript 7, and IL-3 receptor-α chain.[7]

Asthma

Numerous studies have documented the involvement of DC populations in human asthma. The following discussion highlights key recent findings. It has been

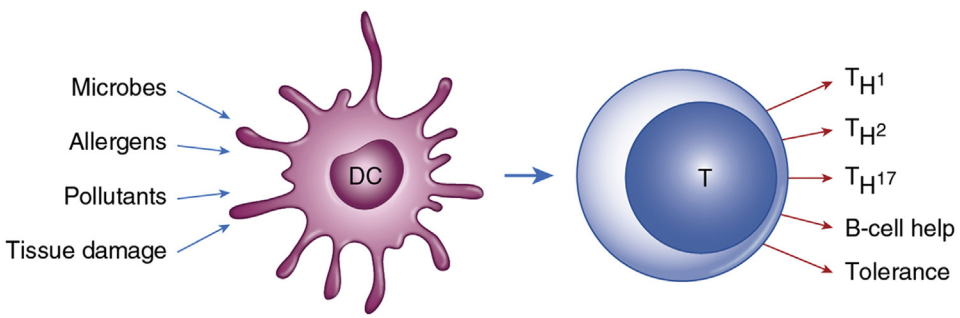

Figure 1 – *Dendritic cells integrate information received from inhaled antigen and the local tissue, which they transfer together with antigenic peptides to responding T cells. This has a profound effect on the nature of the ensuing T-cell response. DC = dendritic cell; T = T cell; T_H = T helper cell.*