Cell-mediated Adaptive Immune Defense of the Lungs

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Cell-mediated adaptive immune responses contribute to defense against all classes of pulmonary pathogens and are essential against viruses, mycobacteria, and fungi, including *Pneumocystis carinii*. Adaptive responses depend on sequential pairwise interactions between three cell types: T cells, natural killer (NK) cells, and dendritic cells (DC). Differential expression of specific adhesion molecules and chemokines regulates the location and timing of these interactions. Primary adaptive responses are triggered by immature myeloid DC, which carry antigen from the lungs to regional lymph nodes. Antigen presentation by these mature DC is required to activate naive CD4 T cells, which are essential to generate polarized type 1 or type 2 effector responses and for robust immunologic memory. Inflammation recruits NK cells and DC that interact in a contact- and tumor necrosis factor-α–dependent fashion within injured tissues to initiate immune response polarization. NK cells exposed to IL-12 favor survival of DC that prime for Th1 responses, whereas NK cells exposed to IL-4 do not exert DC selection, leading to tolerogenic or Th2 responses. Naive αβ T cells, NK cells, and DC also amplify secondary adaptive responses to previously encountered pathogens. However, secondary responses are accelerated because memory T cells can migrate directly to infected tissues where they can be activated without strenuous costimulatory requirements. Additionally, previous pulmonary infections or immune responses increase numbers of lung DC and populate the lungs with clones of memory B cells and T cells that are immediately available to respond to infections.

Keywords: T lymphocyte; natural killer cell; dendritic cell; adhesion molecules; chemokines

The adaptive immune system protects the lungs against an astounding range of pathogens, whether invading our alveoli or hiding within our own cells, and it does so with increased efficiency each time we encounter the same or related organisms. These properties—versatility, exquisite specificity, and memory—contribute to defense against all classes of pulmonary pathogens. Adaptive responses are essential for intracellular pathogens, notably mycobacteria, whose clearance requires classical macrophage activation; for viruses, which have evolved many ways to evade or neutralize innate immunity; and for fungi, which combine the explosive growth potential of bacteria with the sophistication of a eukaryotic genome.

The attributes of versatility, specificity, and memory depend on a complex interplay of many cell types and multiple soluble factors. Adaptive immune responses build upon and shape innate immune responses. Although this article focuses on the cell-mediated adaptive response, it is overly simplistic to believe that the innate and adaptive arms act in a purely sequential or unidirectional manner. Cell-mediated responses are also modulated by humoral immunity, via activating and inhibitory Fc receptors present in varying combinations on all leukocytes. This interplay between immune cells and factors generally proceeds smoothly, but its complexity provides many opportunities for immunocompromise that may be global or circumscribed.

This article reviews current concepts of cell-mediated adaptive immunity in normal host defense of the adult lung. Primary immunodeficiencies that present in childhood (1) are not considered. The focus is on recent discoveries that may not be familiar to nonimmunologists but that are likely to affect clinical practice soon. This article is divided into three sections. The first section introduces T cells, natural killer (NK) cells, and dendritic cells (DC), each of which has distinct subsets with complementary actions. The second section describes how integrated immune responses are defined by polarized cytokine secretion. The third section analyzes the spatial and temporal organization of cell-mediated responses.

MÉNAGE À TROIS: THE INTERDEPENDENT LIVES OF T CELLS, NK CELLS, AND DC

αβ T Cells: The Costs and Rewards of a Thymic Education

Most T cells relevant to lung host defense express a T-cell antigen receptor (TCR) containing αβ variable chains that permit recognition of short peptides. Precursors of αβ T cells are recruited from the marrow to the thymus under the influence of P-selectin and the chemokine CXCL12 (2, 3). Progressing through distinct micro-environments due to differential expression of specific chemokines (4), thymocytes undergo first positive and then negative selection, assuring that their TCR respond to self–major histocompatibility (MHC)/peptide complexes, but not so strongly as to be overtly autoreactive. Negative selection depends on thymocyte exposure to so-called "promiscuous expression" of genes usually specific to other tissues. This unique property of thymic medullary epithelial cells is driven in part by the AIRE transcription factor (5). During thymic maturation, T cells randomly develop expression of CD8, allowing antigen recognition in the context of class I MHC, or CD4, linking recognition to class II MHC. The tiny fraction ($< 5\%$ of input) that successfully completes thymic education begins the life of a naive T cell wandering from bloodstream to lymph nodes and back again in search of antigenic stimulation.

Thymic output is not accelerated by peripheral T lymphopenia. Most evidence indicates that the thymus begins to involute in late childhood (6, 7), reducing entry of naive T cells into the circulating T-cell pool. Total pool size is maintained in health by homeostatic proliferation, driven by recognition of self-MHC and IL-7 for naive T cells and largely by IL-15 for memory CD8 cells (8). CD4 memory requires organized lymphoid tissue and IL-7, but how it is maintained is uncertain (8). The diversity of the

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αβ T cell repertoire is another matter. T-cell diversity depends on MHC background (because thymic selection deletes clones) and on one's unique history of antigen exposures and infections. Repeated viral infections select for T cells with broad cross-reactivity but can result in drop-out of some CD8 clones (9). Thymus-independent T cells exist, especially in the gut, but they cannot compensate for loss of the thymus due to skewed TCR diversity and limited recirculatory capacity (10). These processes steadily impoverish T-cell diversity, reducing responses to novel infections or immunizations.

γδ T Cells Leave Home Early

All vertebrates possess a second lineage of T cells that bear TCR containing γδ variable chains. γδ T cells are distinctive in several ways (Table 1). First is their ontogeny. γδ T cells leave the thymus during fetal or early postnatal life in clonal waves and persist in adulthood as self-replicating peripheral populations. Second, they chiefly occupy different tissue niches than αβ T cells. γδ T cells are rare in blood and lymphoid tissues but are common in the gut and other mucosa, including the airways. Third, γδ TCR variable chains often show limited diversity, in extreme cases being essentially invariant. This finding implies that γδ T cells should see limited classes of highly conserved antigens. The nature of such antigens is controversial, with evidence for autoreactivity to stress-induced self proteins and for polyclonal reactivity to small pathogen-derived products such as isoprenylpyrophosphates (11, 12). Both types of stereotypic recognition are reminiscent of the innate immune system.

The true role of γδ T cells is uncertain and likely differs depending on anatomic location and TCR clonality (which are inter-related) (13, 14). To the degree that γδ T cells contribute to host defense, they do so early in infections. In murine models, γδ T cells play a nonredundant role in *Nocardia* lung infection (15) and are needed to prevent dissemination of *Klebsiella* (16), but their marked response to mycobacteria seems to be nonessential. Most data indicate that γδ T cells play an immunoregulatory role mediated by cytolysis. Gene-targeted mice lacking γδ T cells show exaggerated inflammation to multiple pathogens, including *Mycobacterium tuberculosis* (17). Human γδ T cells show greater TCR diversity than do γδ T cell of mice, complicating extrapolations between species. γδ T cells have been best studied in asthma pathogenesis, and γδ T-cell deficiencies leading to opportunistic infections in humans have not been identified.

NK and NK T Cells: Licensed to Kill

Natural cytotoxicity, the ability to rapidly lyse cells without the previous antigen-presentation required by cytolytic CD8 or CD4 T cells, is a feature of two classes of lymphocytes, classical NK cells and NK T cells (Table 1). Classical NK cell are a highly heterogeneous population of large granular lymphocytes that lack variable antigen receptors. NK T cells also display natural cytotoxicity but express αβ TCR of limited diversity (18). The signature role of both types of NK cells is to lyse cells having reduced expression of class I MHC ("missing self"). This ability makes NK cells crucial in defense against cytopathic viruses (especially herpesviruses) that induce this loss of expression as a means of evading CD8 T-cell attack (19).

NK cells sense this MHC reduction using a polymorphic series of invariant receptors. In humans, these consist of killer inhibitory receptors specific for HLA-A, -B, and -C allotypes and of CD94/NKG2A heterodimers that recognize the nonclassical HLA-E molecule. Individual NK clones usually express inhibitory receptors of only one type; in this way, the NK system can detect reductions in even a single class of HLA molecule. More recently, NK cells have been recognized to choose targets based not only on missing self but also by integrating signals from activation receptors that can sense ligands induced on host cells by stress. The history of evolving thought on NK recognition has recently been summarized (20).

NK cells contribute to defense against *Cryptococcus neoformans* and *Aspergillus fumigatus* (21, 22). Because NK cells possess TLR3 and TLR9 receptors, they can respond directly to bacteria and viruses. NK cells express CX3CR1 (fractalkine receptor), which by analogy with monocytes should mediate constitutive migration to noninflamed tissues; high levels of L-selectin to permit entry into lymph nodes; and (unlike T cells) CD11b/CD18 (Mac-1), which may facilitate recruitment to sites of inflammation (23). NK cells and NK T cells also play key immunoregulatory roles that bridge innate and adaptive responses.

DC Lead a Dual Lifestyle

DC are monocytic cells that undergo an abrupt midlife conversion (24). Immature DC (iDC) constantly imbibe and ingest antigens, retaining them without presentation. In healthy lungs, iDC reside in airway epithelium, alveolar septae, and around pulmonary vessels (25) but rarely within alveoli. Once activated

TABLE 1. T-CELL AND NK CELL SUBSETS INVOLVED IN LUNG HOST DEFENSES

Characteristic	αβ T cells	γδ T cells	NK T cells	Classical NK cells
TCR variable chains	αβ	γδ	αβ	None
MHC restriction	Class I or II	Class IB (some)	CD1d	Class I (suppresses)
Expressed TCR diversity	Large	Limited	Limited	None
Antigen recognition	Peptide plus MHC	Protein, unusual nonproteins	α-galactosyl ceramide, self-glycolipids	Multiple activation receptors sensing cellular stress
Phenotype	CD4+ or CD8+	Mostly CD4−, CD8− (CD8 αα+ in gut)	CD4+ or CD4−, CD8−	CD4−, CD8−
Frequency in blood (% of lymphocytes)	65–70%	1–5%	0.01–1%	5–7%
Distribution in absence of inflammation	Blood and lymphoid tissue	Epithelia, blood	Liver, spleen, bone marrow	Blood, spleen
Autoreactivity	Only in T_R subset	Yes	Yes	No
Effector functions	Cytokine release (Th1/Th2) Cytolysis (mostly CD8+)	Cytolysis Cytokine release (Th1 > Th2)	Cytolysis Cytokine release (Th1 > Th2)	Cytolysis
Principal roles in lung defense	Immunoregulation, cytokine secretion	Immunoregulation, immunosurveillance	Polarization of immune responses	Immunoregulation, Lysis of virally infected cells

Adapted from data in or cited by References 13, 14, 18, 35.

by TLR stimulation or proinflammatory cytokines, DC express the chemokine receptor CCR7 and migrate to lymph nodes while increasing expression of costimulatory molecules (26) to become highly efficient antigen-presenting cells.

Two phenotypes of DC are important for lung host defenses: myeloid DC (mDC) express TLR4, TLR1, TLR2, and TLR3, allowing them to be activated by LPS, mycopeptides, and viral RNA with production of IL-12; by contrast, plasmacytoid DC (pDC) express TLR9 and TLR7, permitting them to respond to bacterial DNA and viruses with production of IFN-α. Whether these DC phenotypes represent stable lineages arising from distinct precursors remains controversial (27, 28); additional DC phenotypes inhabit the skin (Langerhans cells) and spleen.

THREE WAYS TO RESPOND: POLARIZED ADAPTIVE IMMUNE RESPONSES

One of the most instructive paradigms of contemporary immunology is the dichotomy between type 1 and type 2 responses, which are defined by cytokine production. They are often called T helper 1 (Th1) and T helper 2 (Th2) responses based on the CD4 T-cell subsets that constitute the bulk of these polarized responses, but similar cytokine profiles can be produced by NK and CD8 T cells and by eosinophils, respectively. Type 1 responses are characterized by secretion of IFN-γ but also produce IL-2, tumor necrosis factor–α, and granulocyte/macrophage colony-stimulating factor. Type 1 responses classically activate macrophages to kill intracellular pathogens, particularly *M. tuberculosis*. Type 1 responses are especially crucial in the lungs because alveolar macrophages require exogenous interferons to activate STAT1-dependent effector mechanisms (including nitric oxide generation) in response to bacterial or viral products (29). Type 2 responses are characterized by the production of IL-4, IL-5, IL-9, IL-10, and IL-13. These cytokines favor antibody production with class switching to IgE and IgG_4 and downregulate type 1–induced inflammation. Because much of the lung damage in viral infections can be mediated by the type 1 response itself, such downregulation may preserve lung integrity, but type 2 responses also favor fibrosis (30).

Polarization of individual T-cell clones solidifies via chromatin modification that is ultimately due to fate-determining transcription factors (T-Bet for Th1 cells, GATA-3 for Th2 cells) (31). Moreover, the phenotype of the entire response becomes self-reinforcing because products of these polarized responses inhibit each other. Thus, IFN-γ suppresses growth of Th2 cells, and IL-10 blocks cytokine production by Th1 cells. These opposing effects predict that ineffectual responses to specific pathogens may result from inappropriate immune response polarization. This is the case, as shown by the disparate responses of inbred mouse strains to *C. neoformans* (32), providing graphic validation in the lung of principles established in extrapulmonary leishmanial and helminthic infections. Heterologous immunity, the unanticipated responses by memory T cells to putatively unrelated viruses due to cross-reacting epitopes, provides other examples (9).

One puzzle underlying this dichotomy is the initial source of IFN-γ or IL-4. Although stochastic cytokine production by activated T cells is a sufficient explanation *in vitro*, during *in vivo* responses a more relevant source is the very rapid (< 6 h) production of IFN-γ by classical NK and NK T cells or of IL-4 by NK T cells. It was originally postulated that mDC and pDC were pre-programmed to polarize naive αβ T cells toward Th1 and Th2 phenotypes, respectively (33), but subsequent data show that mDC and pDC can induce type 1 or type 2 responses, depending on antigen dose and the state of DC maturation (34).

Recently, a third phenotype of T-cell response has been identified, that of regulatory T (T_R) cells. This response is largely mediated by a distinctive CD25+ CD4 T-cell subset under the control of the Foxp3 transcription factor (35). T_R cells principally develop from thymocytes that have intermediate self-reactivity but can also be produced peripherally during lymphopenia or chronic antigenic stimulation. T_R can suppress type 1 or type 2 responses mediated by CD4 or CD8 αβ T cells via an undefined, contact-dependent mechanism. The effector mechanism of CD25+ CD4 T_R cells may involve apoptosis of the target and is independent of IL-10 and TGF-β, but other T-cell subsets with suppressive properties act via these cytokines (35).

ARRANGING LIAISONS: ORGANIZING IMMUNE RESPONSES IN TIME AND SPACE

DC and Naive αβ T Cells Meet in Lymph Nodes

Naive αβ T cells transit from bloodstream to lymph nodes for two reasons: mechanistically, because their pattern of adhesion and chemokine receptor expression (L-selectin and CCR7, respectively) permit entry only there, via high endothelial venules, and not into sites of inflammation (4, 36); and teleologically, because survival of T cells depends on finding an antigen that will activate them and on IL-7 produced in the node by mesenchymal cells. Without both signals, naive αβ T cells survive only weeks in a T-cell–replete host. This arrangement matches the design of DC, which enter lymph nodes via afferent lymphatics once mature and ready to present antigens. Mature DC alone express the proper combination of antigen plus MHC (signal 1) and costimulatory molecules (signal 2) to activate naive αβ T cells efficiently. Hence, during primary immune responses, naive αβ T cells are activated in organized lymphoid tissue.

Lymph node anatomy facilitates these interactions. Chemokines arriving from the inflamed site are siphoned to the high endothelial venules by a reticulin network; fibroblastic reticular cells form corridors that direct lymphocyte traffic (37). Bronchus-associated lymphoid tissue (BALT), which is unencapsulated but organized tissue that increases with age, may facilitate the development of specific pulmonary immune surveillance and responses. BALT was originally considered part of a common mucosal immune system, together with lymphatic tissue in the gut, Waldeyer's ring, and the urogenital tract. However, the unique combinations of adhesion molecules needed for lymphocyte entry into BALT (38) implies that it supports tissue-specific homing.

DC and NK Cells: A Life-Altering, Potentially Fatal Rendezvous

During lung inflammation, DC are replenished by rapid recruitment from the blood (39) in a process that depends on CCR2 and CCR6 but not endothelial selectins (40). NK cells are also rapidly recruited and engage mDC in a reciprocally regulating interaction. Via IL-12, mature mDC activate NK cytolytic function and production of tumor necrosis factor–α and IFN-γ, whereas activated NK cells enhance mDC maturation and IL-12 secretion (41). The net result is selection of DC that polarize naive αβ T cells to a type 1 phenotype. Conversely, exposure of NK cells to IL-4 (from NKT cells, eosinophils, or mast cells) impairs their development of cytolytic function, cytokine secretion, and ability to promote efficient mDC maturation. The net result is DC that induce a type 2 or tolerogenic response (35, 41). NK cells seem to be particularly sensitive to stress, and loss of their immunoregulatory functions may contribute to relative immunocompromise in the perioperative period and likely in other critically ill patients (42).

A subset of activated human NK cells also eliminates any remaining iDC (41). Like the carnage of thymic education, this

seemingly wasteful solution has survival advantage. By lysing iDC replete with tolerogenic antigens derived from apoptotic host cells, the process assures that emigrating DC are pulsed exclusively with antigens specific to the infection. NK cells can also migrate to lymph nodes in a CCR7-independent manner to influence T-cell priming (43).

Secondary Pulmonary Immune Responses: The Benefits and Risks of Persistence

In contrast to naive αβ T cells, effector αβ T cells have much reduced requirements for activation, which can be fulfilled by a wide range of cytokine-activated cell types. Moreover, effector T cells express diverse adhesion receptors that permit them to enter inflamed tissues effectively. Murine lymphocyte subsets differ in their dependence on specific adhesion receptors for recruitment to the lungs (e.g., CD8 T cells and Th1 CD4 cells strongly depend on endothelial selectins, whereas γδ T cells do not) (44, 45). These data, plus existing human studies (46), suggest that it might be possible to manipulate immune responses therapeutically by altering expression of combinations of specific adhesion molecules or chemokines, or their receptors.

Resolving infections leave the lungs populated with immune cells that can accelerate future local immune responses. B cells and functional DC persist for months after antigenic stimulation (47, 48). Similarly, viral pneumonias in mice induce persistence of large numbers of specific T-cell clones, with CD8 T cells remaining longer than CD4 T cells. These CD8 clones do not proliferate in the lungs but express specific antiviral activity and high levels of receptors typically associated with acute activation (49), leading them to be called "persistently activated T cells." An attractive but unproven possibility is that similar mechanisms explain the exuberant BALT and large numbers of lymphocytes, especially CD8 T cells, seen in advanced chronic obstructive pulmonary disease (50). If so, data on heterologous immunity and T-cell clonal deletion (9) imply that the response of individual patients to respiratory viruses may be inappropriately severe or feeble due to the cumulative impact of their infectious history on their own adaptive immune responses.

CONCLUSIONS

This review of cell-mediated adaptive immunity provides several lessons. Immune responses, like the most rewarding experiences of human life, arise from relationships between individuals. The nature of these relationships can evolve at different stages of life history; they can have unanticipated and at times unpredictable outcomes; and their consequences may be long-lasting, leading to commitment, or even, perhaps, to death. Success requires being in the right place at the right time; this the immune response attempts to guarantee by carefully controlling the expression of adhesion receptor/ligand and chemokine/chemokine receptor pairs. The immune system is regulated by consensus; no single cell type controls the entire adaptive response, and attempts to do so are often vigorously rebuffed. Finally, the response to even seemingly trivial respiratory pathogens is modulated by past immunologic history because memory T cells, in the words of Marcel Proust, "touch epochs that are immensely far apart, separated by the slow accretion of many, many days—in the dimension of Time."

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