

Chapter 2

Lung Dendritic Cells and Pulmonary Defence Mechanisms to Bacteria

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2.1 General Function of Dendritic Cells in the Lungs

Dendritic cells (DCs) are potent antigen-presenting cells (APCs) that have emerged as key regulators of adaptive immunity (Lambrecht and Hammad 2009). The general function of lung DCs is to recognize and pick up foreign antigens at the outskirts of the body, and subsequently migrate with their cargo to the draining mediastinal lymph nodes where antigen is processed into immunogenic peptides and displayed onto MHCI and MHCII molecules for presentation to naïve T cells. In fact these cells should be seen as specialized cells of the mononuclear phagocyte system that have evolved from the cells of the innate immune system to control adaptive immunity that came later in evolution (Banchereau and Steinman 1998). Dendritic cells express all the pattern recognition receptors shared with phagocytes of the innate immune system, yet at the same time also have the machinery to talk to T cells and B cells and relay information about the type of antigen to these cells, so that a tailor-made adaptive response is induced and long-term memory is initiated.

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As these cells respond to many noxious stimuli from both the outside world (pathogen associated molecular patterns or PAMPs) and from within (danger associated molecular patterns or DAMPS) and at the same time closely communicate with lung structural cells like alveolar epithelial cells (AECs), endothelial cells and fibroblasts, it has been proposed that they could be crucial players in many lung diseases, particularly where T cell responses are involved in initiation of maintenance of the disease (van Rijt et al. 2005). Only very recently, there have been the first case reports of patients that display defects in the DC system. These DC-deficient patients are at risk of severe viral skin infections and pulmonary infections with atypical mycobacteria (Vinh et al. 2010 #13365; Bigley et al. 2011 #13358). Our own experiments employing DC-deficient mice have elucidated a crucial role for these cells in the induction of protective immunity to influenza virus, via induction of both CD4 and CD8 T cell responses (GeurtsvanKessel et al. 2008). Similar conclusions have been reached in models of tuberculosis and bacterial lung infections with *Staphylococci* and *Bordetella pertussis* (Dunne et al. 2009; Jiao et al. 2002; Martin et al. 2011). Conversely, DCs are also heavily involved in maintaining immunopathology in which T cells play a predominant role, the best example being the mucosal inflammation seen in asthma and COPD. An emerging concept, that we cover in this chapter, is that there are several subsets of DCs in the lungs of mice, rats and humans that share many functional features among species. The most simple discrimination is based on a division of two subsets of conventional CD11c^{hi} DCs (separated into a CD11b⁺ subset and a CD11b[−] subset, the latter also expressing CD103 and langerin), a CD11c^{dim} plasmacytoid DC subset, and a fourth class of inflammatory DCs that derive from monocytes under conditions of inflammation and also express CD11b as well as some inflammatory monocyte markers like Ly6C, FcεRI and CD64 (see Fig. 2.1 for an overview of mouse DC subsets).

2.2 Brief Overview of Pulmonary Innate Defence Mechanisms Needed to Understand DC Biology

2.2.1 Mechanical and Physical Pulmonary Defence Mechanisms

The inspired air is contaminated with toxic gases, particulates and microbes. The first line of defence of the lung is made up of the complex physical shape of the conducting upper and lower airways causing a highly turbulent airflow that facilitates the impaction, sedimentation and deposition of particulate matter and microorganisms on the mucosa, followed by the removal of these deposited particles by the mucociliary blanket and/or the physical expulsion from the respiratory tract by sneezing, coughing or swallowing (Barber et al. 2003). The action of the mucociliary blanket is a dynamic and complexly regulated escalator for bringing inhaled particles to the throat so that they can be swallowed. The conducting airways are lined with ciliated epithelium and the structure and function of the cilia in propulsing mucus have been extensively studied (Cowan et al. 2001; de Iongh and Rutland 1995; Santamaria

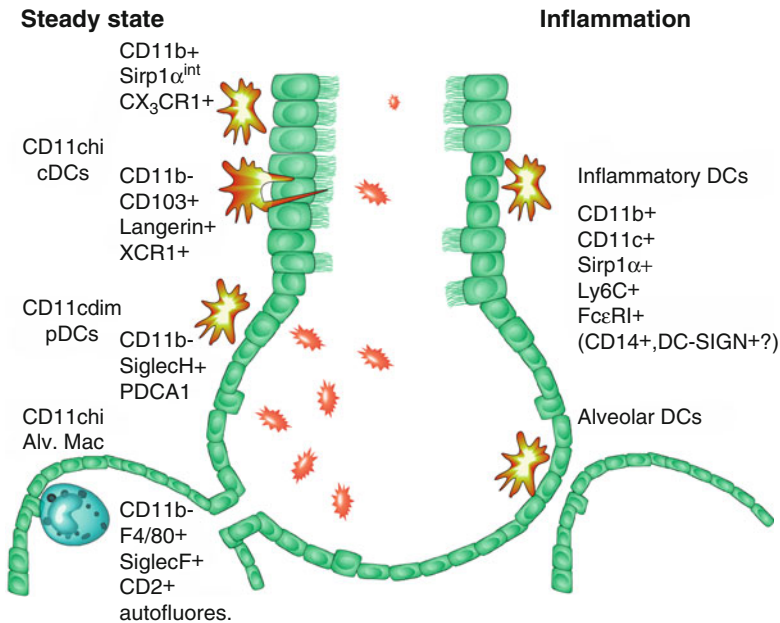


Fig. 2.1 In the left of the diagram the subsets of DCs found in steady state are depicted. These include conventional (c)DCs and plasmacytoid (p)DCs. Conventional DCs are still subdivided in two large families, one being CD11b positive, the other negative for CD11b. Under conditions of inflammation there is immediate recruitment of monocytes that can also give rise to inflammatory type DCs. These are also CD11b positive, yet still express discrete set of markers to discriminate them from CD11b⁺ cDCs

et al. 2008). The correct movement of cilia and function of the mucociliary escalator also depends on the low viscosity of the periciliary fluid layer, physically a hydrated sol layer, allowing sufficient separation between the apical side of the epithelium and the viscous mucous blanket covering the cilia (Matsui et al. 1998a, b). Any discussion on the biology of dendritic cells, such as their potential to take up antigen, needs to be seen in the light of this complex mucociliary escalator. Dual photon live imaging studies on oxygenated tracheal explants have shown that DCs can extend long dendrites into the lumen of the trachea, and these movements seem to follow the direction of the mucociliary blanket (Hammad et al. 2009).

2.2.2 Humoral Innate Immune Mechanisms in the Lung

Innate immune defences are evolutionary conserved pathways of defence that kill microbes in a generic pathway, often relying on the recognition and antagonism of common motifs in microbial proteins or lectins, the so-called pathogen-associated molecular patterns that are so crucial for the function of the microbe that their

antagonism leads to loss of pathogenicity. Just like acquired or adaptive immunity, innate immunity consists of a humoral and a cellular part.

Humoral innate defence mechanisms are elaborate in the lung and consist of lactoferrin, lysozyme, defensins, complement, cathelicidins and collectins (Bals and Hiemstra 2004). These molecules can be produced by airway structural cells or by recruited innate immune cells like neutrophils and macrophages (see below). Surfactant protein A and D are collectins that opsonize bacteria and viruses like influenza. As humoral innate immunity developed early in evolution, many of its component mediators like defensins, surfactant proteins and complement have the potential to influence the function of dendritic cells in the airways (Awasthi et al. 2011; Brinker et al. 2001; Castellano et al. 2004; Ryan et al. 2011; Yang et al. 1999).

2.2.3 Cellular Innate Immune Mechanisms in the Lung

The cellular arm of innate immunity in the lung is primarily made up of alveolar macrophages and recruited neutrophils (Fig. 2.1). Alveolar macrophages serve an important function in the phagocytosis, killing and/or neutralization of inhaled particulate antigens. Resident alveolar macrophages continuously encounter inhaled substances due to their exposed position in the alveolar lumen. These cells are packed with enzymes, metabolic products and cytokines that are vital to defence of the alveolar space but can potentially damage the alveolo-capillary membrane. To avoid collateral damage to type I and type II AECs in response to harmless antigens, they are kept in a quiescent state, producing little inflammatory cytokines (Holt 1978). Alveolar macrophages also actively suppress the function of interstitial lung DCs that are situated in the alveolar septa (Holt et al. 1988). It has been estimated previously that the pool of alveolar macrophages can handle up to 10^9 intratracheally injected bacteria before there is spillover of bacteria to DCs and before adaptive immunity is induced (MacLean et al. 1996). Elegant studies have demonstrated that in vivo elimination of alveolar macrophages using clodronate-filled liposomes lead not only to overt inflammatory reactions to otherwise harmless particulate and soluble antigens (Thepen et al. 1989), but also to an increased sensitivity to bacterial, fungal and viral infection. In their exposed position, alveolar macrophages serve the first line of defence against inhaled pathogens not only by directly acting as the main phagocytes, but also as an important producer of pro-inflammatory chemokines, cytokines, lipid mediators bioactive mediators that recruit other cell types to the lung (see Fig. 2.2).

In contrast to alveolar macrophages that reside in the lung and serve an immediate line of innate defence against inhaled pathogens, neutrophils are recruited within minutes after inoculation of microbes into the lung. The main function of neutrophils is phagocytosis and killing of microbes, particularly fungi like *Aspergillus* sp. and *Pneumocystis jirovecii*. They can also kill microorganisms through release of alfa-defensins and lysozyme. Neutrophil killing function depends on oxidative

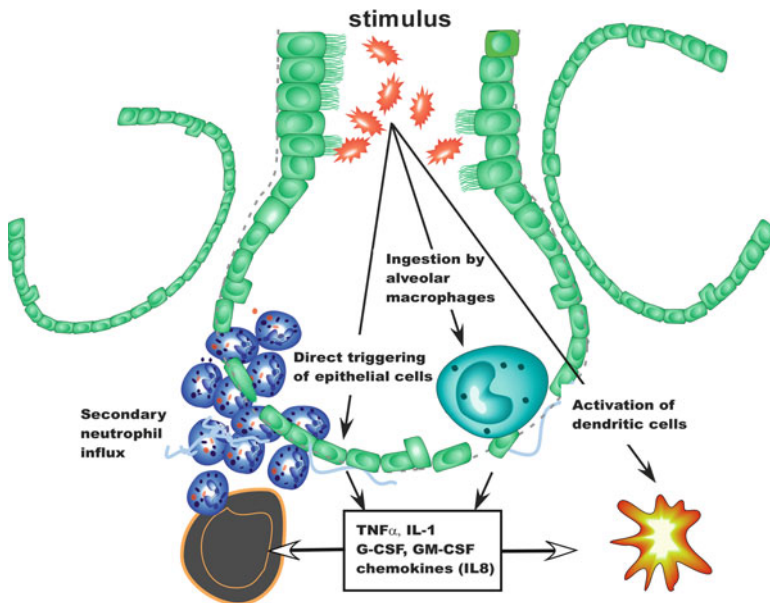


Fig. 2.2 When a pathogen is inhaled, it will directly trigger the lung epithelial cells to produce chemokines and cytokines that attract and activate neutrophils, monocytes and DCs. Additionally, pathogens will also trigger a response from alveolar macrophages that first phagocytose the pathogen, but also induce an innate immune response, to further recruit neutrophils and monocytes. The entire inflammatory milieu with its cytokines, and endogenous danger signals will act to activate the DC network

enzymes like those of the NADPH oxidase system and myeloperoxidase. Once recruited, neutrophils can also further enhance more neutrophil recruitment through the production of cytokines (IL-1, TNF α , IL-6) as well as through release of calcium-binding proteins of the S100 family (S100A8, A9 and A12) that act on the receptor for advanced glycation end products (RAGE receptor). Neutrophils also communicate directly with DCs through Mac-1 or CD11b expressed on their surface interacting with DC-SIGN on DCs (Cheung et al. 2010; van Gisbergen et al. 2005b), as well as through release of cytokines, chemokines, neutrophil elastase, S100 family members and possibly through ROS production (Cheung et al. 2010; Tang et al. 2012). In this way, neutrophils might function as danger sensors that communicate the presence of infection to DCs and instruct them to tailor ensuing immune responses to the type of pathogen (van Gisbergen et al. 2005a). As only one example, neutrophils are recruited early after infection of mice with *Mycobacterium tuberculosis*. Depletion of neutrophils using monoclonal antibodies leads to reduced migration of DCs to the mediastinal lymph nodes and delayed antimycobacterial defence mechanisms (Blomgran and Ernst 2011). As with alveolar macrophage depletion, depletion of neutrophils lowers the threshold by which lung DCs seem to capture bacteria and fungi (Park et al. 2010).

2.3 Induction of Innate Immune Responses in the Lung Also Leads to DC Recruitment

The above mechanisms of innate defence act in a coordinated fashion. Although a single aspect of the innate defence system can be triggered directly through recognition of foreign PAMPs, the innate defence mechanisms are often induced simultaneously via triggering of common receptors on both phagocytes (for cellular defences) and epithelial cells (for inducing the production of humoral innate defence mechanisms). The most famous pattern recognition receptors (PRRs) belong to the family of toll-like receptors (TLRs, TLR1–11), NOD-like receptors, RIG-I like receptors and C-type lectin receptors (Kawai and Akira 2010). These receptors recognize particular conserved PAMPs on specific groups of microbes. The archetypical TLR4 is expressed at the cell surface and recognizes the Gram-negative cell wall component LPS, whereas TLR2 recognizes peptidoglycan and TLR5 recognizes bacterial flagellin. The endosomal TLR receptors TLR3 recognize double-stranded RNA, TLR7 and TLR8 single-stranded RNA and TLR9 unmethylated CpG motifs (Kawai and Akira 2010). The exact cellular localization and downstream signalling pathways of these pathways have been studied extensively over the last few years and several clinical primary immunodeficiency syndromes have been brought back to deficiencies in one of the signalling intermediates of these pathways (Ku et al. 2007).

Many studies have shown that administration to the lung of either purified individual TLR ligands or whole (inactivated) bacteria or viruses leads to massive recruitment of DCs to the lungs, through the production of chemokines that can attract DCs (McWilliam et al. 1994; Stumbles et al. 2001). DCs reside in an immature state in the periphery of the lung, where they are located strategically to detect inhaled particulate and soluble antigen. Within the DC population, cDCs and pDCs differ in their TLR expression pattern, but relatively little is known about this in the lung. The expression profile of TLRs on DCs seems however to be organ-specific. A study has compared the expression of TLR4 and TLR9 on lung and spleen cDCs, and found that lung DCs expressed higher levels of TLR4 but only very low levels of TLR9, whereas spleen DCs had the opposite pattern (Chen et al. 2006). Immgen array gene expression data have shown that mouse CD103⁺ DCs mainly express TLR3, whereas CD11b⁺CD103⁻ DCs mainly express TLR2 and TLR7 (Desch et al. 2011). Both subsets express low levels of TLR4 in steady state.

In human lung, type 1 mDC and BDCA3⁺ type 2 mDC express mRNA transcripts for TLR1, TLR2, TLR3, TLR4, TLR6 and TLR8. In response to TLR2 and TLR4 ligands mDC type 1 and mDC type 2 release proinflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-8), whereas only type 1 mDCs produce proinflammatory cytokines in response to TLR3 triggering. Human lung pDC express TLR7 and TLR9 and release proinflammatory cytokines and type I interferon in response to imiquimod and CpG oligonucleotides (Demedts et al. 2006).

2.4 Indirect Activation of the DC Network by Epithelial Cells

Although direct recognition of foreign PAMPs by PRRs is the most likely explanation how DCs respond to foreign antigen, it is now clear that recognition of PAMPs by the closely epithelial cells is at least as important in activating the lung DC network. This conclusion was reached by studying the in vivo response of lung DCs to the TLR4 agonist endotoxin (LPS), in bone marrow chimeric mice that lacked TLR4 exclusively on either radiosensitive hematopoietic cells or radioresistant epithelial cells. In the absence of TLR ligation, lung DCs demonstrated a sessile behaviour. Provision of LPS led to a dramatic increase in motility and antigen sampling behaviour that led to crawling of DCs in between basal epithelial cells. Strikingly, instruction for this pattern of motility required TLR4 triggering of epithelial cells and not on DCs directly (Hammad et al. 2009). Lung epithelial cells also produce the essential chemokines that chemoattract immature cDCs and inflammatory monocytes to the site of antigen exposure. For lung DC recruitment to inflammatory stimuli, several chemokines and cytokines have been implicated. The chemokine CCL20 and epithelial β -defensin are ligands for CCR6 expressed by immature (lung) DCs, and bronchial epithelial cells produce these factors in response to TLR ligation, C-type lectin triggering, allergen inhalation, virus infection, as well as exposure to environmental pollutants (Hammad et al. 2009; Kallal et al. 2010; Nathan et al. 2009; Reibman et al. 2003). However, a careful study of the contribution of the CCR6 pathway to steady-state cDC lung biology has not been performed. It seems that under conditions of inflammation, other chemokine receptor interactions come into play. When sensitized mice receive an aerosol challenge with the relevant protein antigen, CCR2, and not CCR5 or CCR6 seems to be the relevant chemokine receptor for causing the accumulation of lung DCs, although this might be predominantly through its capacity to release monocytic precursors from the bone marrow (Robays et al. 2007). When a challenge with sheep red blood cells is given in the lungs, CCR2 directs DC precursors from the blood to the lung interstitium, whereas CCR6 directs their transit from the interstitium to the airway (Osterholzer et al. 2005). In rats, a CCR1/CCR5 antagonist however blocks bacteria-induced DC recruitment to the lung (Stumbles et al. 2001). Freshly isolated respiratory mucosal DC respond to different CC chemokines, (MCP-1, -4, RANTES and eotaxin), complement cleavage products and *N*-formyl-peptides (McWilliam et al. 1996).

The precise role of the CX3CR1 receptor in lung DC recruitment following inflammation is currently unknown. Exposure of mouse lungs with cigarette smoke leads to CX3CL1 upregulation in the lungs. As the receptor CX3CR1 is present on many inflammatory cells like monocytes and CD11b+ cDCs, it is likely that this pathway could also contribute to recruitment of inflammatory type DCs to the lung (Jakubzick et al. 2008; McComb et al. 2008). Another trigger for recruitment of DCs to the lungs under inflammatory conditions is the production by bronchial epithelial cells of a homodimer of the p40 subunit of IL-12 (Walter et al. 2001). Viral as well as mycobacterial infection of the lung as well as allergic inflammation induces this p80 form of IL-12, and it was shown recently that lung DCs infected

with *M. tuberculosis* use an alternatively spliced variant of the *IL-12rb1* gene to generate a shorter IL-12R β 1 isoform (IL-12R β 1 Δ TM) that promotes the responsiveness of the classical IL-12R β 1 to IL-12 p80 (Robinson et al. 2010). Whether different DC subsets would employ this mechanism of migration to the lung differentially and how this receptor is regulated is currently unknown.

Epithelial cells not only make chemokines that attract immature monocytes or DCs, they also produce critical maturation cytokines like IL-1, GM-CSF and TSLP that can activate the recruited monocytes to differentiate in DCs and induce their maturation into fully competent APCs capable of interacting with naïve T cells (for more detailed discussion, see Lambrecht and Hammad 2012).

2.5 Induction of Adaptive Cellular Antimicrobial Immunity by DCs

Dendritic cells are potent APCs that have emerged as key regulators of adaptive immunity (Lambrecht and Hammad 2009). The general function of lung DCs is to recognize and pick up foreign antigens at the outskirts of the body, and subsequently migrate with their cargo to the draining mediastinal lymph nodes where antigen is processed into immunogenic peptides and displayed onto MHCI and MHCII molecules for presentation to naïve T cells. Once DCs transport their antigenic cargo to the draining lymph nodes, they induce the proliferation and differentiation of naïve T cells into particular types of T cell responses (see Fig. 2.3). Discrete types of T helper cells provide crucial help for different parts of the innate and adaptive immune response (Zhu et al. 2010). Th1 cells make IFN γ and mainly provide help to monocytic cells, including macrophages and dendritic cells, and thus enforce killing of intracellular pathogens, and at the same time enforce opsonization of these through provision of B cell help. Conversely, Th2 cells make IL-4, IL-5 and IL-13 to provide help to eosinophils, mast cells and basophils to eliminate complex helminths, and at the same time induce IgG1 and IgE from B cells to arm the basophils and mast cells with effector potential. For a long time since the original description of the Th1/Th2 concept, it has been unclear which subtype of T cell help was important for inducing neutrophilic responses and protection from extracellular pathogens like fungi. This gap has been breached recently by the discovery of the cytokines IL-17 and IL-22 that are produced by Th17 cells that induce neutrophilic inflammation, production of defensins by epithelial cells and are important for clearance of fungi and extracellular bacteria (Ouyang et al. 2008).

The precise signals that induce different types of Th lineage commitment of naïve T cells have been intensely studied (Zhu et al. 2010). APCs can provide different levels and quality of signal 1 (peptide-MHC), signal 2 (costimulatory molecules) and signal 3 (instructive cytokines) to naïve T lymphocytes upon antigen encounter and triggering of their PPRs (Banchereau and Steinman 1998) (see Fig. 2.4). When stimulated through the unique TCR, naïve CD4⁺ T cells differentiate into Th1 cells in the presence of high amounts of IL-12. IL-12 instructs Th1 development via

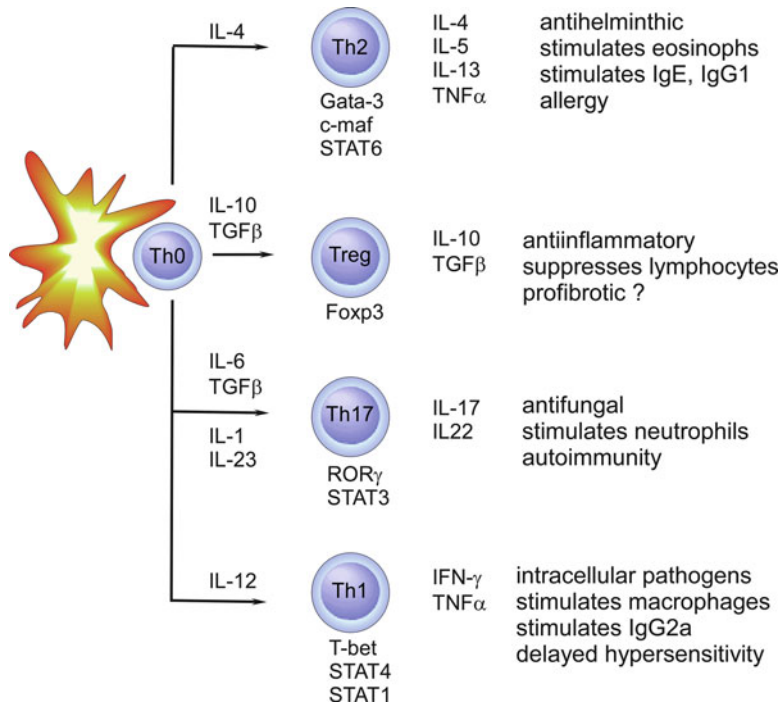


Fig. 2.3 When faced with a pathogen, DCs can induce many types of T helper responses based on their potential to produce polarizing cytokines. The functions of the ensuing T cells and the cytokines mediating effector functions are depicted

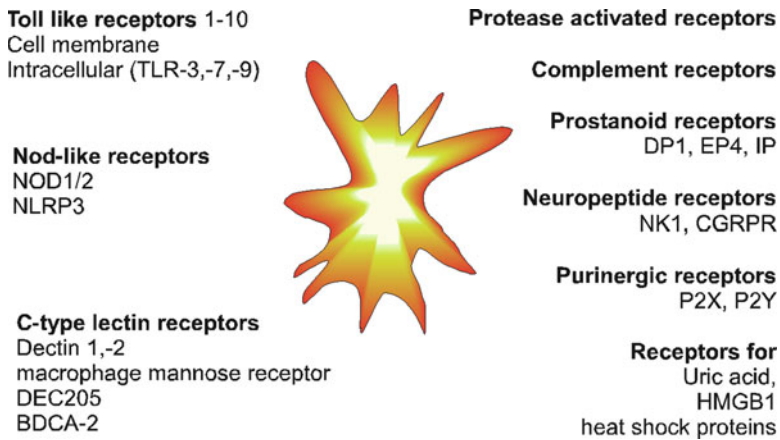


Fig. 2.4 Expression of 'danger' receptors by dendritic cells (DCs). DCs express the highly conserved receptors of the innate immune system also expressed by macrophages such as Toll-like receptors (TLRs), Nucleotide Oligomerization Domain (NOD-like) receptors and C-type selectin receptors (Left side of figure). These receptors react to foreign pathogen-associated molecular patterns (PAMPs). In addition, DCs express numerous receptors for inflammatory mediators and necrotic debris, the so-called damage-associated molecular patterns (DAMPs) (right side of figure).

activation of STAT4 and the lineage instructing transcription factor T-bet. IL-17-producing cells are induced when exposed to a cocktail of cytokines including TGF β , IL-6 and IL-1 α/β , while IL-23 further enhances the proliferation of these cells. The Th17 lineage-specific transcription factor ROR γ t enforces Th17 characteristics in naïve T cells, and is induced by the cocktail of cytokines instructive to their development. The mechanisms leading to Th2 cell differentiation *in vivo* are still poorly understood, but in most instances require a source of IL-4 to activate the transcription factors STAT6 and GATA-3, and a source of IL-2, IL-7 or TSLP to activate the transcription factor STAT-5 (Kopf et al. 1993; Le Gros et al. 1990; Paul and Zhu 2010; Seder et al. 1992; Zheng and Flavell 1997). Despite the overwhelming evidence that IL-4 is necessary for most Th2 responses, DCs were however never found to produce IL-4 and it was therefore long assumed that Th2 responses would occur by default, in the absence of strong Th1- or Th17-instructive cytokines in the immunological DC-T cell synapse, or when the strength of the MHCII-TCR interaction, or the degree of costimulation offered to naïve T cells is weak (Constant et al. 1995; Jankovic et al. 2004; Lambrecht et al. 2000; Stumbles et al. 1998). In this model, naïve CD4 T cells were the source of instructive IL-4. In an alternative view, IL-4 is secreted by an accessory innate immune cell type, like NKT cells, eosinophils, mast cells or basophils that provide IL-4 *in trans* to activate the Th2-differentiation program (Ben-Sasson et al. 1990). In the lung allergic response to house dust mite allergen, we have recently found that basophils help DCs to induce Th2 immunity by providing an important, but not essential source of IL-4 (Hammad et al. 2010).

Lung DCs are also essential in instructing the selection and expansion of CD8 cytotoxic T cells that recognize virus-infected cells, cells infected with intracellular bacteria and tumourally transformed cells via presentation of endogenous cellular antigen on the MHCI complex (GeurtsvanKessel et al. 2008). An important conceptual point is that DCs do not have to be infected themselves to perform this task but can phagocytose virally infected or transformed cells and use the process of cross-presentation to present the exogenous antigen into their MHC-I loading machinery. In the lungs, antigen cross-presentation seems to be a unique feature of the subset of CD103+ DCs (Desch et al. 2011; GeurtsvanKessel et al. 2008). Once activated by DCs and CD4 T cell help, cytotoxic T cells can lyse and kill infected cells in a process requiring granzyme and/or perforin, or kill target cells in an FasL and/or TRAIL-dependent manner, causing apoptotic cell death in targets (Hufford et al. 2011).

The potential of DCs to boost very effective antibacterial immunity might be applied clinically in the future. One such example could be in the eradication of hard-to-eliminate pathogens from colonized airways, such as seen in *Pseudomonas* infection in CF or bronchiectasis patients. In a recent study, it was shown that DCs pulsed with the *Pseudomonas aeruginosa* major constitutive outer membrane porin protein F (OprF) protected mice against *P. aeruginosa* infection and inflammation. Upon adoptive transfer *in vivo*, porin-pulsed dendritic cells (DCs) induced Th1-mediated resistance to infection and associated inflammatory pathology caused by either the PAO1 strain or a clinically isolated mucoid strain, highlighting the pivotal contribution of DCs to vaccine-induced protection (Peluso et al. 2010). Expansion of local DC numbers by cytokines that stimulate their growth and or function might also be

a feasible strategy. In mice, overexpression of GM-CSF from the BCG vaccine strain led to enhanced protection from mycobacterial infection by accelerated priming of antigen-specific CD4⁺ T cells in the mediastinal lymph nodes and increased migration of activated CD4⁺ T cells into the lung (Nambiar et al. 2010).

2.6 Dendritic Cells and Humoral Immune Mechanisms in the Lung

Humoral immunity plays a predominant role in protecting from severe infections with encapsulated bacterial strains. Antibodies are well known for their neutralizing effects on secondary infections and this is the principle of most vaccinations against childhood infections. During a primary infection however, antibodies, some of which have broad spectrum specificity (the so-called natural antibodies) also have the capacity to activate complement and opsonize bacterial cell walls and capsules, hence facilitating clearance of the bugs. Antibodies of the IgA and IgG class are actively secreted into the airway lumen via the action of the polymeric Ig receptor. Airway luminal IgA is an important defence against viral entry. More and more evidence suggests that DCs also control crucial aspects of humoral immunity, by directly interacting with B cells or by providing crucial T cell help of immunoglobulin class switching through stimulation of T follicular helper cells (T_{FH}). Lung DCs can promote the production of IgA in a process dependent on TGF β (Naito et al. 2008). Intratracheal injection of the mucosal adjuvant cholera toxin B subunit also induces DC-dependent IgA class switching (Smits et al. 2009). In contrast to gut epithelial DCs, a recent study on lung DCs identified both RALDH1 and RALDH2 enzymes that promote retinoic acid production, involved in IgA class switching. Both subsets of lung cDCs had equal levels of RALDH activity (Guilliams et al. 2010).

Elegant studies by Snapper et al. have demonstrated that dendritic cells pulsed with pneumococcal antigens can induce antibodies directed against pneumococcal polysaccharides, and lead to neutralizing immunity upon adoptive transfer (Colino et al. 2002, 2009). Along the same lines, but potentially more clinically applicable, adenoviral overexpression of the DC growth factor Flt3L was able to boost anti-pneumococcal antibody responses, leading to elimination of nasal carriage rates in mice (Kataoka et al. 2011).

2.7 Organized Lymphoid Structures and Bronchiectasis

The organized accumulation of lymphocytes in lymphoid organs serves to optimize both homeostatic immune surveillance, as well as chronic responses to pathogenic stimuli (Cupedo and Mebius 2005). During embryonic development, circulating hemopoietic cells gather at predestined sites throughout the body, where they are subsequently arranged in T and B cell-specific areas, thus leading to the formation

of secondary lymphoid organs (SLOs) like lymph nodes and spleen. In contrast, the body has a limited second set of selected sites that support neo-formation of organized lymphoid aggregates in adult life. However, these are only revealed at times of local, chronic inflammation when the so-called tertiary lymphoid organs (TLOs) appear. Just like in lymph nodes and spleen, areas of TLOs are characterized by the formation of specialized high endothelial venules and the organized production of chemokines leads to cellular organization of T cells and B cells in discrete area. In humans, TLOs have been observed in the joint and lung of rheumatoid arthritis (Rangel-Moreno et al. 2006), around the airways of COPD patients (Hogg et al. 2004) and in the thyroid (Marinkovic et al. 2006). Certain infectious diseases are also accompanied by formation of TLO. Influenza virus infection of the respiratory tract leads to the formation of inducible bronchus-associated lymphoid tissue (iBALT) that supports T and B cell proliferation and productive immunoglobulin class switching in germinal centres (GCs) (GeurtsvanKessel et al. 2009; Moyron-Quiroz et al. 2004). Tertiary lymphoid follicles or iBALT is very frequently seen in tubular bronchiectasis, and the close association with bronchi might explain the obstruction of small bronchioles and airway obstruction often seen. Formation of TLOs could be the result of chronic colonization of bronchiectatic airways by microbes, and indeed it has been proposed that latent adenoviral infection is a cause of follicular bronchiectasis (Bateman et al. 1995 #13360). However, in one school of thought, TLO formation can also be seen as a source of self-specific autoantibodies and a reflection of an underlying auto-immune component to disease. In TLO associated with RA bronchiectasis, one has indeed seen the production of pathogenic antibodies to citrullinated proteins (Rangel-Moreno et al. 2006). Whatever the mechanism of induction or the pathogenic role of TLO structures, it has been shown that DCs are necessary for their maintenance in response to influenza virus infection, vaccinia virus infection and chronic LPS administration. The reasons for this is that DCs express lymphotoxin $\alpha 1\beta 2$ that stimulates local stromal cells to produce chemokines that keep T and B cell together in a logical context as also seen in SLOs like spleen and lymph nodes.

2.8 Antiinflammatory Pathways

With its large surface area, the lung is a portal of entry for many pathogens as inhaled air is contaminated with infectious agents, toxic gases and (fine) particulate matter. At the same time, inhaled microbes and toxic substances can gain easy access to the bloodstream across the delicate alveolar-capillary membrane. Innate and adaptive immune defence of this vulnerable barrier is not easy and needs to be tightly controlled as too much edema, inflammation and cellular recruitment will lead to thickening of the alveolar wall and will jeopardize the diffusion of oxygen, vital to life. Considering the large surface area of the respiratory epithelium and the volume of air inspired on a daily basis, it is remarkable that there is so little inflammation under normal conditions, suggesting the presence of regulatory mechanisms that act to protect the gas-exchange mechanism. Following even severe

bacterial or viral infection, a return to homeostasis is the usual outcome. Understanding the conditions by which lung immune homeostasis is regulated might be crucial to advance our insight into the pathogenesis of inflammatory lung diseases caused by chronic bacterial colonization (as seen in bronchiectasis) or chronic infections (as seen in TB). One type of cell that has received particular attention in suppressing immune responses in the lung is the alveolar macrophage. Alveolar macrophages adhere closely to AECs at the alveolar wall and are separated by only 0.2–0.5 μm from interstitial DCs. In macrophage-depleted mice, the DCs have a clearly enhanced antigen-presenting function (Holt et al. 1993). When mixed with DCs in vitro, alveolar macrophages suppress T cell activation through release of NO (mainly in rodents), prostaglandins, IL-10 and TGF β . Alveolar macrophages also express CD200R, an inhibitory receptor that regulates the strength of innate immunity to inhaled pathogens. Another cell type that has received a lot of attention is the regulatory T cell or Treg. Natural Tregs express high levels of CD25 and express the lineage-specific transcription factor Foxp3 (Hori et al. 2003). These cells are generated in the thymus and have a natural reactivity for self-antigens as well as some foreign antigens, and mainly suppress autoimmunity (Watanabe et al. 2005). Induced Tregs are generated when DCs encounter self-antigen in the periphery or upon chronic immune stimulation. It is assumed that these induced Tregs serve to dampen overt immune activation to stimuli that cannot be fully eliminated, a typical example being chronic helminth infections or mycobacterial infections (Grainger et al. 2010). It is also possible that failure of Treg function at a certain stage of the disease contributes to ongoing inflammation that might ultimately progress to fibrosis. In this regard it is a striking observation that Tregs also make TGF β as part of their suppressive program. TGF β might be at the crossroads of immunoregulation and fibrosis initiation. Dendritic cells from mycobacteria-infected mice seem to induce large numbers of Treg cells that have a broad anti-inflammatory function, even to inert allergens (Leepiyasakulchai et al. 2012).

Finally, immune regulation might also stem from changes in stromal cells of the airways, such as epithelial cells. Airway epithelial cells play a predominant role in deciding whether or not an acute or chronic stimulus like endotoxin is recognized or not (Hammad et al. 2009). Epithelial cells express many PRRs and the sensitivity of these can be regulated through negative regulators of signalling. Finally, some epithelial-derived cytokines like IL-37 have an intrinsically anti-inflammatory effect on innate immunity in the lung (Nold et al. 2010). It is currently unknown if defects in these counterregulatory mechanisms are involved in maintenance of inflammation in patients with lung infections, and whether these pathways mainly work by affecting the function of lung DCs.

2.9 Conclusion

There has been great progress in our knowledge of innate and adaptive immune responses in the lung, it is increasingly clear that DCs control many aspects of the innate and adaptive immune response to bacterial lung infection.

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References

- Awasthi S, Madhusoodhanan R, Wolf R (2011) Surfactant protein-A and toll-like receptor-4 modulate immune functions of preterm baboon lung dendritic cell precursor cells. *Cell Immunol* 268:87–96
- Bals R, Hiemstra PS (2004) Innate immunity in the lung: how epithelial cells fight against respiratory pathogens. *Eur Respir J* 23:327–333
- Banchereau J, Steinman RM (1998) Dendritic cells and the control of immunity. *Nature* 392:245–252
- Barber CM, Curran AD, Fishwick D (2003) Impaired cough reflex in patients with recurrent pneumonia. *Thorax* 58:645–646; author reply 646
- Bateman ED, Hayashi S, Kuwano K, Wilke TA, Hogg JC (1995) Latent adenoviral infection in follicular bronchiectasis. *Am J Respir Crit Care Med* 151:170–176
- Ben-Sasson SZ, Le Gros G, Conrad DH, Finkelman FD, Paul WE (1990) Cross-linking Fc receptors stimulate splenic non-B, non-T cells to secrete interleukin 4 and other lymphokines. *Proc Natl Acad Sci U S A* 87:1421–1425
- Bigley V, Haniffa M, Doulatov S, Wang XN, Dickinson R, McGovern N, Jardine L, Pagan S, Dimmick I, Chua I et al (2011) The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. *J Exp Med* 208:227–234
- Blomgran R, Ernst JD (2011) Lung neutrophils facilitate activation of naive antigen-specific CD4+ T cells during Mycobacterium tuberculosis infection. *J Immunol* 186:7110–7119
- Brinker KG, Martin E, Borron P, Mostaghel E, Doyle C, Harding CV, Wright JR (2001) Surfactant protein D enhances bacterial antigen presentation by bone marrow-derived dendritic cells. *Am J Physiol Lung Cell Mol Physiol* 281:L1453–L1463
- Castellano G, Woltman AM, Schena FP, Roos A, Daha MR, van Kooten C (2004) Dendritic cells and complement: at the cross road of innate and adaptive immunity. *Mol Immunol* 41:133–140
- Chen L, Arora M, Yarlagadda M, Oriss TB, Krishnamoorthy N, Ray A, Ray P (2006) Distinct responses of lung and spleen dendritic cells to the TLR9 agonist CpG oligodeoxynucleotide. *J Immunol* 177:2373–2383
- Cheung DS, Ehlenbach SJ, Kitchens RT, Riley DA, Thomas LL, Holtzman MJ, Grayson MH (2010) Cutting edge: CD49d+ neutrophils induce FcepsilonRI expression on lung dendritic cells in a mouse model of postviral asthma. *J Immunol* 185:4983–4987
- Colino J, Shen Y, Snapper CM (2002) Dendritic cells pulsed with intact Streptococcus pneumoniae elicit both protein- and polysaccharide-specific immunoglobulin isotype responses in vivo through distinct mechanisms. *J Exp Med* 195:1–14
- Colino J, Chattopadhyay G, Sen G, Chen Q, Lees A, Canaday DH, Rubtsov A, Torres R, Snapper CM (2009) Parameters underlying distinct T cell-dependent polysaccharide-specific IgG responses to an intact gram-positive bacterium versus a soluble conjugate vaccine. *J Immunol* 183:1551–1559
- Constant S, Pfeiffer C, Woodward A, Pasqualini T, Bottomly K (1995) Extent of T cell receptor ligation can determine the functional differentiation of naive CD4 T cells. *J Exp Med* 182:1591–1596
- Cowan MJ, Gladwin MT, Shelhamer JH (2001) Disorders of ciliary motility. *Am J Med Sci* 321:3–10
- Cupedo T, Mebius RE (2005) Cellular interactions in lymph node development. *J Immunol* 174:21–25
- de Jongh RU, Rutland J (1995) Ciliary defects in healthy subjects, bronchiectasis, and primary ciliary dyskinesia. *Am J Respir Crit Care Med* 151:1559–1567

- Demedts IK, Bracke KR, Maes T, Joos GF, Brusselle GG (2006) Different roles for human lung dendritic cell subsets in pulmonary immune defense mechanisms. *Am J Respir Cell Mol Biol* 35:387–393
- Desch AN, Randolph GJ, Murphy KM, Gautier E, Kedl R, Lahoud M, Caminschi I, Shortman K, Henson PM, Jakubczik CV (2011) Efferocytic CD103+ pulmonary dendritic cells selectively acquire and present apoptotic cell-associated antigen. *J Exp Med* 208(9):1789–1797
- Dunne PJ, Moran B, Cummins RC, Mills KH (2009) CD11c+ CD8alpha+ dendritic cells promote protective immunity to respiratory infection with *Bordetella pertussis*. *J Immunol* 183:400–410
- GeurtsvanKessel CH, Willart MA, van Rijt LS, Muskens F, Kool M, Baas C, Thielemans K, Bennett C, Clausen BE, Hoogsteden HC et al (2008) Clearance of influenza virus from the lung depends on migratory langerin+ CD11b- but not plasmacytoid dendritic cells. *J Exp Med* 205:1621–1634
- GeurtsvanKessel CH, Willart MA, Bergen IM, van Rijt LS, Muskens F, Elewaut D, Osterhaus AD, Hendriks R, Rimmelzwaan GF, Lambrecht BN (2009) Dendritic cells are crucial for maintenance of tertiary lymphoid structures in the lung of influenza virus-infected mice. *J Exp Med* 206:2339–2349
- Grainger JR, Smith KA, Hewitson JP, McSorley HJ, Hargus Y, Filbey KJ, Finney CA, Greenwood EJ, Knox DP, Wilson MS et al (2010) Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-beta pathway. *J Exp Med* 207:2331–2341
- Guilliams M, Crozat K, Henri S, Tamoutounour S, Grenot P, Devilard E, de Bovis B, Alexopoulou L, Dalod M, Malissen B (2010) Skin-draining lymph nodes contain dermis-derived CD103(–) dendritic cells that constitutively produce retinoic acid and induce Foxp3(+) regulatory T cells. *Blood* 115:1958–1968
- Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN (2009) House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat Med* 15:410–416
- Hammad H, Plantinga M, Deswarte K, Pouliot P, Willart MA, Kool M, Muskens F, Lambrecht BN (2010) Inflammatory dendritic cells—not basophils—are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. *J Exp Med* 207:2097–2111
- Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, Pare PD (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 350:2645–2653
- Holt PG (1978) Inhibitory activity of unstimulated alveolar macrophages on T-lymphocyte blastogenic responses. *Am Rev Respir Dis* 118:791–793
- Holt PG, Schon-Hegrad MA, Oliver J (1988) MHC class II antigen-bearing dendritic cells in pulmonary tissues of the rat (regulation of antigen presentation activity by endogenous macrophage populations). *J Exp Med* 167:262–274
- Holt PG, Oliver J, Bilyk N, McMenamin C, McMenamin PG, Kraal G, Thepen T (1993) Downregulation of the antigen presenting cell function(s) of pulmonary dendritic cells in vivo by resident alveolar macrophages. *J Exp Med* 177:397–407
- Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. *Science* 299:1057–1061
- Hufford MM, Kim TS, Sun J, Braciale TJ (2011) Antiviral CD8+ T cell effector activities in situ are regulated by target cell type. *J Exp Med* 208:167–180
- Jakubczik C, Tacke F, Ginhoux F, Wagers AJ, van Rooijen N, Mack M, Merad M, Randolph GJ (2008) Blood monocyte subsets differentially give rise to CD103+ and CD103- pulmonary dendritic cell populations. *J Immunol* 180:3019–3027
- Jankovic D, Kullberg MC, Caspar P, Sher A (2004) Parasite-induced Th2 polarization is associated with down-regulated dendritic cell responsiveness to Th1 stimuli and a transient delay in T lymphocyte cycling. *J Immunol* 173:2419–2427
- Jiao X, Lo-Man R, Guermontprez P, Fiette L, Deriaud E, Burgaud S, Gicquel B, Winter N, Leclerc C (2002) Dendritic cells are host cells for mycobacteria in vivo that trigger innate and acquired immunity. *J Immunol* 168:1294–1301
- Kallal LE, Schaller MA, Lindell DM, Lira SA, Lukacs NW (2010) CCL20/CCR6 blockade enhances immunity to RSV by impairing recruitment of DC. *Eur J Immunol* 40:1042–1052

- Kataoka K, Fujihashi K, Oma K, Fukuyama Y, Hollingshead SK, Sekine S, Kawabata S, Ito HO, Briles DE, Oishi K (2011) The nasal dendritic cell-targeting Flt3 ligand as a safe adjuvant elicits effective protection against fatal pneumococcal pneumonia. *Infect Immun* 79:2819–2828
- Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 11:373–384
- Kopf M, Le Gros G, Bachmann M, Lamers MC, Bluethmann H, Kohler G (1993) Disruption of the murine IL-4 gene blocks Th2 cytokine responses. *Nature* 362:245–248
- Ku CL, Picard C, Erdos M, Jeurissen A, Bustamante J, Puel A, von Bernuth H, Filipe-Santos O, Chang HH, Lawrence T et al (2007) IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. *J Med Genet* 44:16–23
- Lambrecht BN, Hammad H (2009) Biology of lung dendritic cells at the origin of asthma. *Immunity* 31:412–424
- Lambrecht BN, Hammad H (2012) The airway epithelium in asthma. *Nat Med* 18:684–692
- Lambrecht BN, Pauwels RA, Fazekas De St Groth B (2000) Induction of rapid T cell activation, division, and recirculation by intratracheal injection of dendritic cells in a TCR transgenic model. *J Immunol* 164:2937–2946
- Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE (1990) Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. *J Exp Med* 172:921–929
- Leepiyasakulchai C, Ignatowicz L, Pawlowski A, Kallienius G, Skold M (2012) Failure to recruit anti-inflammatory CD103+ dendritic cells and a diminished CD4+ Foxp3+ regulatory T cell pool in mice that display excessive lung inflammation and increased susceptibility to *Mycobacterium tuberculosis*. *Infect Immun* 80:1128–1139
- MacLean JA, Xia WJ, Pinto CE, Zhao LH, Liu HW, Kradin RL (1996) Sequestration of inhaled particulate antigens by lung phagocytes: a mechanism for the effective inhibition of pulmonary cell-mediated immunity. *Am J Pathol* 148:657–666
- Marinkovic T, Garin A, Yokota Y, Fu YX, Ruddle NH, Furtado GC, Lira SA (2006) Interaction of mature CD3+ CD4+ T cells with dendritic cells triggers the development of tertiary lymphoid structures in the thyroid. *J Clin Invest* 116:2622–2632
- Martin FJ, Parker D, Harfenist BS, Soong G, Prince A (2011) Participation of CD11c(+) leukocytes in methicillin-resistant *Staphylococcus aureus* clearance from the lung. *Infect Immun* 79:1898–1904
- Matsui H, Grubb BR, Tarran R, Randell SH, Gatzky JT, Davis CW, Boucher RC (1998a) Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. *Cell* 95:1005–1015
- Matsui H, Randell SH, Peretti SW, Davis CW, Boucher RC (1998b) Coordinated clearance of periciliary liquid and mucus from airway surfaces. *J Clin Invest* 102:1125–1131
- McComb JG, Ranganathan M, Liu XH, Pilewski JM, Ray P, Watkins SC, Choi AM, Lee JS (2008) CX3CL1 up-regulation is associated with recruitment of CX3CR1+ mononuclear phagocytes and T lymphocytes in the lungs during cigarette smoke-induced emphysema. *Am J Pathol* 173:949–961
- McWilliam AS, Nelson DJ, Thomas JA, Holt PG (1994) Rapid dendritic cell recruitment is a hallmark of the acute inflammatory response at mucosal surfaces. *J Exp Med* 179:1331–1336
- McWilliam AS, Napoli S, Marsh AM, Pemper FL, Nelson DJ, Pimm CL, Stumbles PA, Wells TNC, Holt PG (1996) Dendritic cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli. *J Exp Med* 184:2429–2432
- Moyron-Quiroz JE, Rangel-Moreno J, Kusser K, Hartson L, Sprague F, Goodrich S, Woodland DL, Lund FE, Randall TD (2004) Role of inducible bronchus associated lymphoid tissue (iBALT) in respiratory immunity. *Nat Med* 10:927–934
- Naito T, Suda T, Suzuki K, Nakamura Y, Inui N, Sato J, Chida K, Nakamura H (2008) Lung dendritic cells have a potent capability to induce production of immunoglobulin A. *Am J Respir Cell Mol Biol* 38:161–167
- Nambiar JK, Ryan AA, Kong CU, Britton WJ, Triccas JA (2010) Modulation of pulmonary DC function by vaccine-encoded GM-CSF enhances protective immunity against *Mycobacterium tuberculosis* infection. *Eur J Immunol* 40:153–161

- Nathan AT, Peterson EA, Chakir J, Wills-Karp M (2009) Innate immune responses of airway epithelium to house dust mite are mediated through beta-glucan-dependent pathways. *J Allergy Clin Immunol* 123:612–618
- Nold MF, Nold-Petry CA, Zepp JA, Palmer BE, Bufler P, Dinarello CA (2010) IL-37 is a fundamental inhibitor of innate immunity. *Nat Immunol* 11:1014–1022
- Osterholzer JJ, Ames T, Polak T, Sonstein J, Moore BB, Chensue SW, Toews GB, Curtis JL (2005) CCR2 and CCR6, but not endothelial selectins, mediate the accumulation of immature dendritic cells within the lungs of mice in response to particulate antigen. *J Immunol* 175:874–883
- Ouyang W, Kolls JK, Zheng Y (2008) The biological functions of T helper 17 cell effector cytokines in inflammation. *Immunity* 28:454–467
- Park SJ, Burdick MD, Brix WK, Stoler MH, Askew DS, Strieter RM, Mehra B (2010) Neutropenia enhances lung dendritic cell recruitment in response to *Aspergillus* via a cytokine-to-chemokine amplification loop. *J Immunol* 185:6190–6197
- Paul WE, Zhu J (2010) How are T(H)2-type immune responses initiated and amplified? *Nat Rev Immunol* 10:225–235
- Peluso L, de Luca C, Bozza S, Leonardi A, Giovannini G, Lavorgna A, De Rosa G, Mascolo M, Ortega De Luna L, Catania MR et al (2010) Protection against *Pseudomonas aeruginosa* lung infection in mice by recombinant OprF-pulsed dendritic cell immunization. *BMC Microbiol* 10:9
- Rangel-Moreno J, Hartson L, Navarro C, Gaxiola M, Selman M, Randall TD (2006) Inducible bronchus-associated lymphoid tissue (iBALT) in patients with pulmonary complications of rheumatoid arthritis. *J Clin Invest* 116:3183–3194
- Reibman J, Hsu Y, Chen LC, Bleck B, Gordon T (2003) Airway epithelial cells release MIP-3alpha/CCL20 in response to cytokines and ambient particulate matter. *Am J Respir Cell Mol Biol* 28:648–654
- Robays LJ, Maes T, Lebecque S, Lira SA, Kuziel WA, Brusselle GG, Joos GF, Vermaelen KV (2007) Chemokine receptor CCR2 but not CCR5 or CCR6 mediates the increase in pulmonary dendritic cells during allergic airway inflammation. *J Immunol* 178:5305–5311
- Robinson RT, Khader SA, Martino CA, Fountain JJ, Teixeira-Coelho M, Pearl JE, Smiley ST, Winslow GM, Woodland DL, Walter MJ et al (2010) *Mycobacterium tuberculosis* infection induces *il12rb1* splicing to generate a novel IL-12Rbeta1 isoform that enhances DC migration. *J Exp Med* 207:591–605
- Ryan LK, Dai J, Yin Z, Megjugorac N, Uhlhorn V, Yim S, Schwartz KD, Abrahams JM, Diamond G, Fitzgerald-Bocarsly P (2011) Modulation of human beta-defensin-1 (hBD-1) in plasmacytoid dendritic cells (PDC), monocytes, and epithelial cells by influenza virus, Herpes simplex virus, and Sendai virus and its possible role in innate immunity. *J Leukoc Biol* 90:343–356
- Santamaria F, Montella S, Tiddens HA, Guidi G, Casotti V, Maglione M, de Jong PA (2008) Structural and functional lung disease in primary ciliary dyskinesia. *Chest* 134:351–357
- Seder RE, Paul WE, Davis MM, Fazekas de St.Groth B (1992) The presence of interleukin 4 during in vitro priming determines the lymphokine-producing potential of CD4+ T cells from T cell receptor transgenic mice. *J Exp Med* 176:1091–1098
- Smits HH, Gloudemans AK, van Nimwegen M, Willart MA, Soullie T, Muskens F, de Jong EC, Boon L, Pilette C, Johansen FE et al (2009) Cholera toxin B suppresses allergic inflammation through induction of secretory IgA. *Mucosal Immunol* 2:331–339
- Stumbles PA, Thomas JA, Pimm CL, Lee PT, Venaille TJ, Proksch S, Holt PG (1998) Resting respiratory tract dendritic cells preferentially stimulate T helper cell type 2 (Th2) responses and require obligatory cytokine signals for induction of Th1 immunity. *J Exp Med* 188:2019–2031
- Stumbles PA, Strickland DH, Pimm CL, Proksch SF, Marsh AM, McWilliam AS, Bosco A, Tobagus I, Thomas JA, Napoli S et al (2001) Regulation of dendritic cell recruitment into resting and inflamed airway epithelium: use of alternative chemokine receptors as a function of inducing stimulus. *J Immunol* 167:228–234
- Tang Y, Guan SP, Chua BY, Zhou Q, Ho AW, Wong KH, Wong KL, Wong WS, Kemeny DM (2012) Antigen-specific effector CD8 T cells regulate allergic responses via IFN-gamma and dendritic cell function. *J Allergy Clin Immunol* 129(6):1611–1620

- Thepen T, Van Rooijen N, Kraal G (1989) Alveolar macrophage elimination in vivo is associated in vivo with an increase in pulmonary immune responses in mice. *J Exp Med* 170:494–509
- van Gisbergen KP, Geijtenbeek TB, van Kooyk Y (2005a) Close encounters of neutrophils and DCs. *Trends Immunol* 26:626–631
- van Gisbergen KP, Ludwig IS, Geijtenbeek TB, van Kooyk Y (2005b) Interactions of DC-SIGN with Mac-1 and CEACAM1 regulate contact between dendritic cells and neutrophils. *FEBS Lett* 579:6159–6168
- van Rijt LS, Jung S, Kleinjan A, Vos N, Willart M, Duez C, Hoogsteden HC, Lambrecht BN (2005) In vivo depletion of lung CD11c+ dendritic cells during allergen challenge abrogates the characteristic features of asthma. *J Exp Med* 201:981–991
- Vinh DC, Patel SY, Uzel G, Anderson VL, Freeman AF, Olivier KN, Spalding C, Hughes S, Pittaluga S, Raffeld M et al (2010) Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood* 115: 1519–1529
- Walter MJ, Kajiwarana N, Karanja P, Castro M, Holtzman MJ (2001) Interleukin 12 p40 production by barrier epithelial cells during airway inflammation. *J Exp Med* 193:339–351
- Watanabe N, Wang YH, Lee HK, Ito T, Wang YH, Cao W, Liu YJ (2005) Hassall's corpuscles instruct dendritic cells to induce CD4+ CD25+ regulatory T cells in human thymus. *Nature* 436:1181–1185
- Yang D, Chertov O, Bykovskaia SN, Chen Q, Buffo MJ, Shogan J, Anderson M, Schroder JM, Wang JM, Howard OM, Oppenheim JJ (1999) Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 286:525–528
- Zheng W, Flavell RA (1997) The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. *Cell* 89:587–596
- Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol* 28:445–489



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