Review article :

Mucosal immune system of the respiratory tract: regulation of tolerance and immune response.

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The respiratory, gastrointestinal and genitourinary systems are internal organs of the body directly open to the external environment. The mucosal linings of the above systems are constantly exposed to diverse foreign antigens, including the unwanted and harmful ones and face the threat of invasion by pathogenic microorganisms. While protecting the body from harmful agents, the mucosa also needs to remain tolerant against innocuous foreign antigens to prevent inflammatory damage to the host and to allow retention of beneficial microbial flora, which serve essential metabolic and immunological functions. This requires a very sophisticated and intricately regulated mucosal immune system.

The lung is by far the largest organ of the body directly in contact with the atmosphere. Nearly 10,000 to 20,000 liters of air is ventilated per day by an adult human through the surface area that is approximately the size of a tennis court (~ 100 m2). Over this enormous surface, the interior of the body is separated from the external environment by a membrane as thin as 1-2 μm (approximately 1/10th of the cell nucleus) [1]. While this permits smooth gas exchange, it makes the respiratory system especially vulnerable to environmental pathogens as well. The structure, cellular disposition and functions of the respiratory tract mucosal immune system allow well-coordinated and tightly regulated immune response with maximum discretionary power to differentiate between harmless and harmful immunogenic materials and respond accordingly. In the absence of noxious agents, the clearance of foreign antigens takes place in a tolerogenic and anti-inflammatory way, which is controlled by co-ordinated efforts of the airway and lung epithelial cells, resident dendritic cells (DCs) and macrophages, along with different regulatory T-cells. Moreover, inflammatory response activated during infections or epithelial damage must subside rapidly after microbial clearance/ killing or repair of tissues to allow uninterrupted gas exchange, thus highlighting the complex regulation of the mucosal immune response in the respiratory tract microenvironment. Inappropriate and uncontrolled acute inflammation may lead to acute respiratory distress syndrome (ARDS), while recurrent or chronic inflammation may result in diseases like asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD)[2]. All these disorders may be accompanied by severe impairment of gas exchange that may end up with respiratory failure. The global mortality due to respiratory failure caused by infections and uncontrolled inflammation is more than 4 million per year [3]. Thus the respiratory tract stands at the edge of wellness and disaster; a small change may result in a large difference and could lead to life-threatening condition. We discuss here the structural organization of the respiratory tract mucosal immune system that allows recognition of various immunologic insults and the different strategies body have evolved to maintain homeostasis in the face of these challenges. We also provide a brief account of how the viral and bacterial pathogens are handled by the antigen presenting cells (APCs) when they breach the epithelial barrier. Finally, we briefly discuss the role of T-regulatory (Treg) cells in mucosal tolerance and the situations where tolerance is broken to give rise to immune response.

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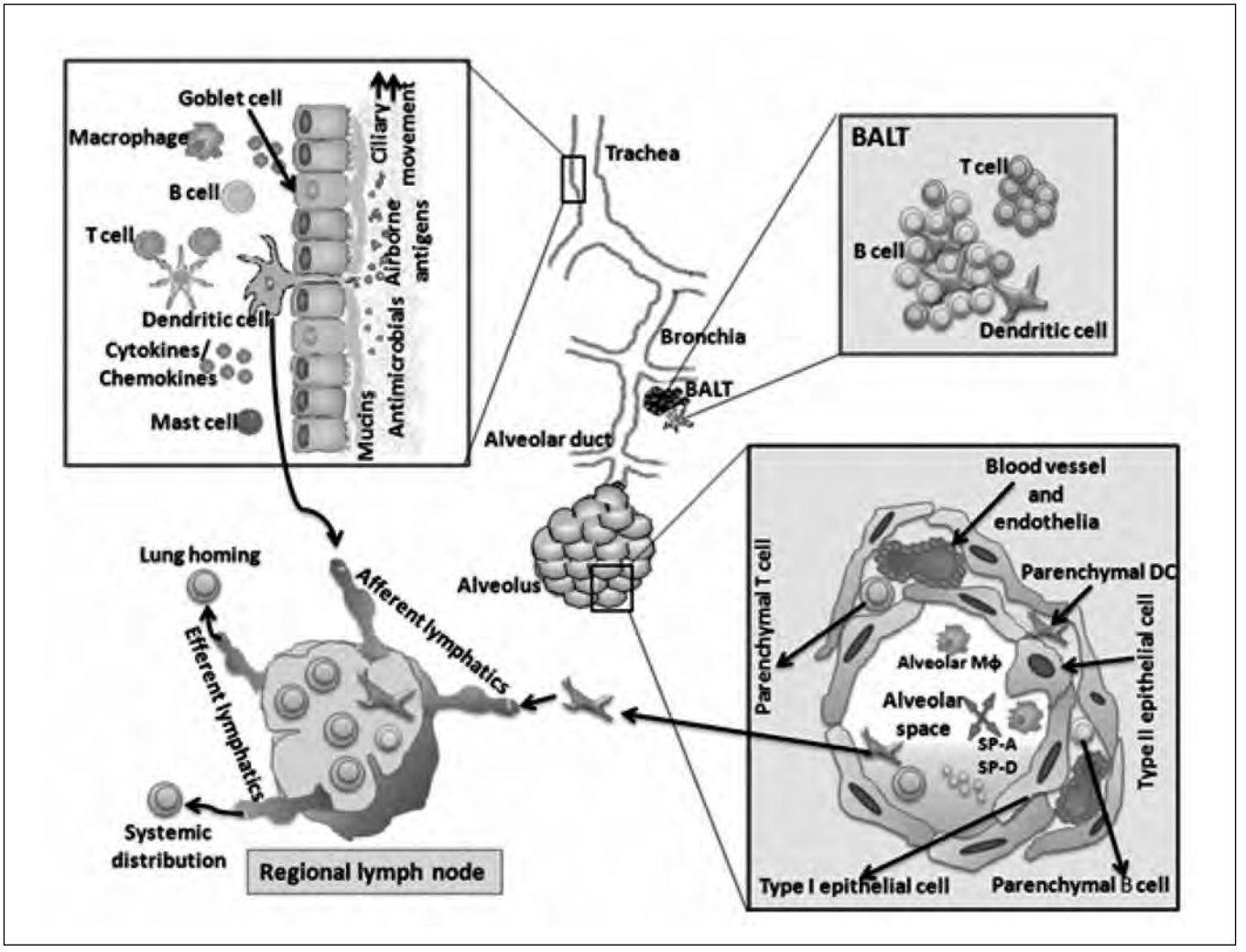
Structure of the respiratory tract mucosal immune system



Mucosal immune system consists of inductive and effector sites. Inductive sites of the human respiratory tract include the palatine tonsils and adenoids in the upper respiratory tract [equivalent to nasopharynx-associated lymphoid tissue (NALT) in rodents] and bronchus-associated lymphoid tissue (BALT) in the lower tract. However, the role of BALT in humans is controversial and it may be an important inductive site only during childhood [4]. BALT was found to be induced (iBALT) under inflammatory conditions, such as human influenza A virus (IAV) infection [5]. At the inductive tissues, antigens are taken up from the luminal to the basolateral side of the epithelial cells by one of the following three regulated mechanisms: M cells may allow transcytosis of antigens without processing them further to be taken up by the subepithelial APCs. A second pathway may be IgG:antigen complexes being transported by receptors in the epithelial cells. In addition, CD103+ lamina propria DCs may directly sample antigens from the lumen by extending peudopods through the epithelial cells [6]. APCs migrate to the parafollicular T cell region of the mucosa-associated lymphoid tissue to present the processed antigens. In the B cell region, germinal center is formed and antibody class- switching takes place to generate surface IgA positive (IgA+) B cells. Nearly 20% of nasal passage lymphocytes are CD3 positive, out of which 50% express CD4 and one third are CD8+ cells. At least two B cell subsets are found in the respiratory tract mucosa. Conventional B2 cells comprise ~25% of all mononuclear cells, while B1 cells (CD5+) constitute only 5% of all B cells [7]. Intriguingly, B1 cells are capable of immunoglobulin (Ig) class switching to IgA+ cells by DCs without T cell help. This is

mediated by direct interaction of DCs with BAFF (B cell activating factor) and APRIL (a proliferation inducing ligand) on B1 cells in presence of interleukin 5 (IL-5) [8]. Antigen-stimulated T cells and surface IgA+ B cells enter the efferent vessels and dispatched to the systemic circulation through the cervical lymph nodes. Finally, these cells home to the mucosal effector sites, which not only include the nasal passages, but also lamina propria (LP) of the gastrointestinal, upper respiratory and reproductive tracts, secretory glandular tissues and the intestinal epithelium. Homing of IgA+ B cells depends on the expression of the chemokine receptor CCR10 on the cell surface and its ligand CCL28 by the mucosal tissues. This results in the so-called common mucosal immune system, which is not found in other immune systems [9]. After reaching the effector site, IgA+ B cells are differentiated into Ig producing plasma cells, in which monomeric IgA and a J-chin are assembled to form polymeric IgA (pIgA). pIgA complexes with its receptor (pIgR) expressed by the mucosal epithelial cells and is transported to the apical side of the cells. Secretory IgA (SIgA) is released into the lumen after partial digestion of pIgR and neutralize extracellular pathogens. pIgA is also able to neutralize intracellular viruses during pIgR-mediaed transport through the cells [10].

Immune recognition at the respiratory tract mucosa

Cells of the respiratory system including the airway epithelial and immune cells, fibroblasts and smooth muscle cells are equipped with a diverse array of germline-encoded receptors to sense a broad range of conserved structural motifs, known as microbe-associated molecular patterns (MAMPs) derived from the resident or invading microbes as well as endogenous host-derived molecules (damage-associated molecular patterns or DAMPs). These are called pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I like receptors (RLRs), C-type lectin like receptors (CLRs) and cytosolic DNA sensors and are expressed on the cells surface or endosomal membrane and in the cytosol (Table 1) [11]. Upon recognition of the ligands, PRRs activate the intracellular signaling pathways and induce appropriate immune responses (clearance response or tolerance) through pro-/anti-inflammatory or regulatory and/or antiviral cytokines expression. The importance of PRRs in the respiratory tract is underscored by altered susceptibility of the knockout mice to infectious and non-infectious diseases and the association of human diseases with genetic polymorphisms involving the PRRs. In addition, their dynamic expression is modulated according to the conditions of the microenvironment. For example, surface expression of TLR4 is downregulated or the receptor is internalized upon exposure to cigarette smoke [12]. PRR expression by the cells of the respiratory system and their relations to various infections and non-infectious diseases are listed in the table below.

Association of pattern recognition receptors with respiratory tract diseases:

Receptor	Cellular expression	Ligand	Association with infectious diseases (provide protection)	Association with non-infectious diseases
TLR-1	AM, cDC, EC,	Triacyl lipopeptide (with TLR-2)	Invasive aspergillosis	Protection from asthma
TLR-2	AM, cDC, EC, endothelial cells, fibroblast, smooth muscle cells	Lipoprotein, peptidoglycan, lipoteichoic acid, endogenous molecules (HMGB1, hyaluronans), *Legionalla pneumophilia LPS*	Legionella pneumophilia, Chlamydia pneumoniae, Streptococcus pneumoniae, Mycoplasma pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans (systemic infection), Pneumocystis jiroveci (formerly Pneumocystis carinii)	Protection from asthma, ALI/ARDS, bleomycin-induced lung fibrosis

TLR-3	cDC, EC, fibroblast, smooth muscle cells	Double stranded RNA	RSV, detrimental role in Influenza A virus infection	Increased allergy, worsens ALI/ARDS
TLR-4	AM, cDC, EC, endothelial cells, fibroblast, smooth muscle cells	Lipopolysaccharide (LPS), RSV coat protein F, pneumolysin, C. pneumoniae HSP-60, endogenous molecules (HSPs; fibronectin, HMGB1, hyaluronans, oxidized lipoproteins, oxidized phospholipids)	*Klebsiella pneumoniae, Hemophilus influenzae, Pseudomonoas aeruginosa (along with TLR5). Mycobacterium tuberculosis, Candida albicans, Aspergilus fumigates*	Increased allergy and asthma (low dose LPS, TLR4 and CD14 loss of function polymorphisms), protects from age-related emphysema, COPD due to cigarette smoke, ALI/ARDS, bleomycin-induced lung fibrosis
TLR5	EC	Bacterial flagellin	*Pseudomonoas aeruginosa (along with TLR4), Legionella pneumophilia, respiratory melioidosis (Burkholderia pseudomallei)*	Improved lung function in cystic fibrosis (loss of function polymorphism)
TLR-6	AM, EC	Diacyl lipopeptide (with TLR-2), Yeast zymosan	*Yersinia pestis, Invasive aspergillosis*	Increased risk of asthma
TLR-7/8	pDC, endothelial cells	Single stranded RNA, imidazoquinoline	Influenza A virus, RSV	Protection from asthma
TLR-9	pDC, fibroblast	CpG DNA motifs	Streptococcus pneumoniae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans (pneumonia)	Protection from asthma
TLR-10	Alveolar epithelium, endothelial cells	unknown		
NOD1	Ubiquitous	iE-DAP	*Staph aureus, Chlamydia pneumoniae, Hemophilus influenza*	
NOD2	Leukocytes, EC	MDP	*Staph aureus, Chlamydia pneumonia*	
NALP	Leukocytes, EC	Anthrax lethal toxin, microbial DNA, pore forming toxin	*Klebsiella pneumonia*	Increased asbestosis and silicosis (NLRP3)
NLRC4 (IPAF)	AM	Bacterial flagellin	*Legionella pneumophilia, Pseudomonoas aeruginosa*	
NAIP5	AM, EC	Bacterial flagellin	*Legionella pneumophilia*	
NLRX1	Mitochondial membrane			
RIG-I	AM, EC	Short dsRNA	Influenza A virus, RSV	
MDA5	AM, EC	Long dsRNA		

Several key points about PRR signaling in the development and progression of respiratory diseases need to be highlighted. Firstly, PRRs exert both protective and deleterious effects on respiratory disorders. A weak constitutive activation of TLRs may be necessary to maintain tissue homeostasis and to avoid emphysema development. But, inflammasome activation by TLRs and/or NLRs in response to microbes DAMPs and cigarette smoke may lead to COPD [2]. TL2 and TLR4 deficient mice are more susceptible to hypoxia-induced acute lung injury (ALI), while TLR3 deficiency confers a survival benefit. Secondly, although multiple PRRs are simultaneously involved in the pathogen recognition and immune response, they may not play equally important role for a particular infection. Thus, TLR9 is more critical than TLR 2 and 4 in the protection against pneumococcal pneumonia, while NLRs, rather than TLRs predominantly contribute to anti-staphylococcal immunity in the lung and RLRs are the key players during viral infections [13]. Thirdly, due to functional redundancy, absence of more than one PRRs or common adaptors of the signaling pathways, such as MyD88 or TRIF exerts more profound effects than a single PRR deficiency. This is supported by the co-operation between TLR 2 and 4 in anti-chlamydial (Chlamydia pneumoniae) immunity and TLR 4 and 5 in the protection against Pseudomonas aeruginosa[14, 15]. Because of their seminal role in the respiratory tract mucosal homeostasis and immune response, TLRs have been targeted for the treatment of respiratory diseases. Administration of underacylated form of Rhodobacter sphaeroides LPS, a TLR4 antagonist, reduced eosinophilia and lymphocytosis and the levels of Th2 cytokines IL-5 and IL-13 in the broncho-alveolar lavage (BAL) fluid of house dust mites (HDM)-induced allergic asthma patients [16]. CpG-ODN (TLR9 agonist) administration, with or without concurrent chemotherapy decreases airway hyperreactivity and inflammation in mice models [17].

The mucosal epithelial cells: a mechanical and immunological barrier

The epithelium of the respiratory tract is at the interface of the human body with inhaled air that contains microbial pathogens and environmental pollutants. Epithelial cells are attached to the neighbouring cells by tight junctions, adherens junction, gap junctions and desmosomes, forming an impermeable mechanical barrier, which protects the body from invading pathogens and also permits maintenance of ionic gradient essential for directional movement of effector molecules. In addition, the epithelial cells also express various PRRs and thus behave as immune sensors. However, the sensing function is prevented from giving rise to chronic inflammatory state by the immunomodulatory activities of the epithelium. Thus the default setting a the state of hyporesponsiveness or tolerance to low doses of antigens or pathogens, achieved by factors intrinsic to the epithelial cells or products of the cells that are active at the site of their origin (cis-acting or autocrine factors) and epithelial-derived mediators acting on other cells (trans-acting factors). With the antigenic/pathogenic dose above a threshold level, the inhibitory microenvironment gives way to a stimulatory one. This implies that loss of immune modulation by the epithelium may lead to chronic inflammatory diseases.

The conducting airways are lined by pseudostratified epithelium comprising of ciliated columnar cells, mucous-secreting goblet cells, club cells (formerly Clara Cells) and undifferentiated basal cells. The alveolar epithelium consists of Type I (AT-I) and Type II (AT-II) pneumocytes. AT-I cells facilitate gas exchange, while AT-II cells produce the surfactant. The cis-acting factors of the epithelium contributing to microbial hyporesponsiveness include mucins and mucociliary clearance, surfactant and cell-intrinsic mechanisms, such as the suppression of TLR signaling. Mucins are high molecular weight glycoproteins predominantly produced by the goblet cells, but also by the club cells and alveolar epithelial cells, which create a physical barrier between the epithelium and the stimulants in the lumen. They also display antimicrobial, antiprotease and antioxidant properties [18]. Mucins are either secreted in the airway lumen or tethered to the apical side of the

epithelial cells. MUC5AC and MUC5B are the most abundantly secreted mucins with the former having inducible expression, while the latter is constitutively expressed. In contrast, MUC1 remains tethered after secretion and functions as a receptor for P. aeruginosa [19]. The surfactant prevents the alveolar macrophages to get in contact with the pathogens, thereby allowing a restricted immune defence. Two surfactant proteins, SP-A and SP-D bind to TLR2 and TLR4 and their co-factors blocking the receptor activation [20]. SP-C on the other hand, binds to LPS. Airway mucosal epithelial TLR signaling is also suppressed by the lack of CD36 (TLR2 co-factor) and MD2 and CD14 (co-factors for TLR4) expression as well as sequestration of TLR4 and TLR5 to the basolateral side of the cells.

Mucosal epithelial cells of the respiratory tract also produce a variety of factors that target DCs, macrophages and lymphocytes and modulate their response. These factors may be grouped according to their functions into factors acting through direct cell-cell contact, local acting cytokines and lipophilic molecules. AT-II cells suppress TNF-α and IL-6 release from LPS-stimulated alveolar macrophages (AMs), which is mediated by CD200 and its receptor expression by the AT-II cells and AMs, respectively [21]. Similarly, PD-L1/PD-1 interaction between the airway epithelial cells (AECs) and CD8+ T cells was shown to increase the clearance of IAV [22]. Epithelial-derived cytokines, such as TGF-beta, IL-25, IL-33 and TSLP play a critical role in the elicitation of a Th2 or T-regulatory immune response and induce mucosal hyperreactivity or tolerance [23]. Other immunosuppressive and immunomodulatory factors produced by the epithelium, which are critical for homeostasis include eicosanoids (lipoxins and prostaglandins), resolvins (Rv) and glucocorticoids [24,25]. Lipoxins A4 and B4 have anti-inflammatory functions delivered by the suppression of NF-κB activation. Epithelial prostaglandin E2 (PGE2) suppresses TNF-α and IL-12, while increasing 1L-10 secretion from LPS-stimulated pulmonary dendritic cells (DCs). Decreased PGE2 levels were found in the sputum of patients suffering from asthma and pulmonary fibrosis. While high PGE2 levels are found under homeostatic conditions, PGI2 is markedly increased during inflammation and exert an anti-inflammatory role. Resolvins are products of ω3-PUFA by the action of epithelial COX-2. RvE1 protects mice from experimental allergic asthma and RvD promotes resolution of ALI in mice. Epithelial-derived glucocorticoid was shown to induce tolerogenic DCs when used along with PGE2.

In addition to its role in SIgA production (described above), mucosal epithelial cells may also promote immune response by other mechanisms [6]. They can process and present antigens by classical (MHC I and II associated) and non-classical (CD1d associated) pathways. In addition, although these cells lack the classical co-stimulatory molecules of APCs (CD80 and CD86), they may express novel members of the B7 family, such as ICOS and B7-H1 and also molecules that are required for epithelial cell-leukocyte cross talk including CD58, E-cadherin, IL-7R, CEACAM1, CEACAM5 and common γ chain. A number of cytokines, chemokines and other mediators are produced by the mucosal epithelium to modulate the immune response. Important among them are DC chemokines CCL20 and CX3CL1, chemokines for neutrophils and monocytes (IL8, ENA-78, MCP-1, GRO-α and GRO-β) and RANTES that attracts different leukocytes. Small cationic antimicrobial peptides like cathelicidins and defensins are abundantly produced by mucosal epithelium and possess multiple immunomodulatory functions, including chemotaxis and pro-inflammatory response. Most of the above studies were carried out with intestinal epithelial cells, but at least some of the factors, if not all are also relevant for respiratory tract mucosal epithelium.

The antigen presenting cells: dendritic cells and macrophages

Respiratory tract has a rich network of DCs and macrophages with specific locations and specialized functions for different subsets to handle constant exposure to a wide variety of environmental

insults. DCs are sentinels of the immune system, which connect the innate and adaptive arms. In the absence of inflammation, three distinct subsets of DCs exist in the lungs: CD11chiCD103+ (CD8 type) cDCs and CD11chi CD11b+ (CD11b type) cDCs DCs constituting conventional DCs (cDCs) and CD11cdim plasmacytoid DCs (pDCs) [26]. In the airway epithelium, a network of CD103+ DCs extends their long protrusions in between the basolateral space, while the lamina propria contains CD11b+ DCs. Both types of DCs are present in the alveolar septa of the lung parenchyma. The conducting airways also contain pDCs, which express Siglec-H, bone marrow stromal antigen 2 (BST-2) and Ly6C. During inflammation, CD11b+ monocyte-derived DCs (MoDCs) are recruited to the lungs and conducting airways. Lung macrophages include well-defined alveolar macrophages (AMs) and the so called interstitial macrophages, which are much less characterized [3]. Differentiation between the subsets of DCs and macrophages often become difficult due to overlap in the marker expression. MoDcs may be differentiated from CD11b+ cDCs by the expression of CD64 and MAR-1, while AMs may be confused with CD11chi cDCs, but also express high levels of F4/80, CD64 and Siglec-F. Recently, zbt46, a transcription factor was identified as a highly specific marker for both cDC subsets [27].

Accumulating evidence suggests a clear division of labour between the DC and nacrophage subsets in the lungs during pulmonary infection. In fact, a particular subset may be beneficial for one infection, but detrimental to the other. DCs play a critical role in viral clearance from the lungs by initiating antiviral CD8+ cytotoxic T cell responses in the draining lymph nodes. Although both CD103+ and CD11b+ DC subsets are readily infected by IAV, the former plays a more critical role in driving CD8 responses, because of better antigen presentation by MHC-I and their capacity to acquire viral antigens from apoptotic cells [28]. Higher efficacy of CD103+ DCs in inducing antiviral CD8 responses is also observed for modified vaccinia poxvirus and Sendai virus. However, during peak viral replication, CD8 responses are predominantly driven by CD11b+ DCs. pDCs do not play a major role in controlling IAV infection, although they may be critical for other viruses, such as pneumonia virus [29]. Monocytes are massively recruited to the lungs and differentiate into interferon-producing MoDcs following IAV infection. Studies have indicated that MoDCs may primarily interact with the effector T cells in the infected tissues rather than inducing T cells in the lymph nodes. However, they may be the predominant cause of immune payhology during IAV infection. AMs are infected early by the viruses like IAV and RSV and actively participate in viral clearance, as underscored by higher viral load and increased mortality in AM-depleted mice. AMs are the principal source of Type I interferons, which possesses antiviral functions and induces cytotoxic activity in the memory CD8+ T cells in a T cell receptor (TCR)-independent way. In addition, IFNs also limit immunopathology of viral infections by suppressing MoDC-induced inflammation [3]. Some infections like RSV may trigger M2-associated (anti-inflammatory) functions in AMs.

Alveolar Macrophages represent the predominant sentinels against bacterial infections. Both CD11b+ cDCs and AMs phagocytose inhaled Mycobacterium tuberculosis (Mtb) early after infection. However, presentation of the Mtb antigens in the regional lymph nodes results in massive proliferation of Treg cells, limiting entry of effector T cells to the lungs. MoDCs infected in the lungs helps to form granulomas and participate in Mtb elimination by producing TNF-α, nitric oxide (NO), IL-1α and IL-1β. These cells are also responsible for Th1 response against Mtb. In contrast, AMs were proposed to have a dual role in Mtb infection. On one hand, they directly kill bacteria by producing NO and reactive oxygen species (ROS). On the other hand, the anti-inflammatory functions of AMs that appear to be beneficial in IAV infection may favour Mtb persistence [30]. Absence of AMs facilitates dissemination of Brucella through infected cDCs and exacerbates inflammation. AMs suppress inflammation not only by limiting bacterial access

to DCs, but also by directly inhibiting antigen presenting function of DCs and by producing IL-10.

Mucosal tolerance in the respiratory tract and its breakdown

Immunologic tolerance is a state of hyporesponsiveness to antigens that prevents the induction of a strong immune response. In the respiratory tract, tolerance to the resident microbial and otherwise harmless environmental antigens is required to prevent the development of frequent or chronic inflammation, which will seriously compromise gas exchange in the alveoli. Although tolerance is significantly achieved by deletion and anergy of antigen-specific T cells, a key role is also played by CD4+ T-regulatory (Treg) cells that suppress effector T cell (Th1/Th2/Th17) functions. Both the thymus-derived natural Treg (nTreg) cells and peripherally-generated inducible Treg (iTreg) cells were found to suppress lung inflammation in the mouse model. However, the iTreg cels are perhaps more important because of their antigen-speficity and quantitatively better suppressive ability on a per-cell basis [31]. Extensive studies in vitro have shown that predominantly three types of iTreg cells, namely Foxp3+, LAP+FoxP3- and IL-10+FoxP3- cells are generated from the naive T cells upon TCR stimulation by APCs. This requires the presence of various combinations of IL-2, TGF-β, retinoic acid (RA) and IL-10 in the microenvironment, provided by the epithelial cells, DCs, macrophages and T cells [32]. Several subsets of different APCs were found to participate in the overall tolerogenic response. Although specific requirements for the generation of different iTreg subsets are not clearly known, Foxp3 expression requires high levels of TGF-β. Experiments in mice have shown that inhalation of pure protein antigens induce iTreg cells, while allergen extracts or contamination of pure antigens with PRR ligands like LPS preferentially give rise to effector T cells [33]. This implies that tissue resident DCs and macrophages are primarily immature and undifferentiated, which tend to produce TGF, RA and/or IL-10 to favour iTreg cell generation. However, their encounter with stimuli that upregulate co-stimulatory molecule expression and pro-inflammatory cytokines induce effector T cells. It is believed that under homeostatic conditions, interstitial macrophages play a central role in the suppressive mechanisms, although AMs also contribute to it. Lung DCs (both Cd103+ and CD11b+ cells), on the other hand, are more stimulatory than regulatory [34]. This is the opposite to what we observe in the gut, where CD103+ DCs are majorly involved in iTReg cell generation. In contrast, lung pDCs tend to induce tolerance and their depletion may abrogate tolerance induction by pure antigens. This was found to be dependent on PD-L1 expression by pDCs [35]. Both DCs and macrophages are capable to produce IL-10, which may either directly suppress effector T cell function or promote IL10+Foxp3- iTreg cell generation. However, IL-10 producing DCs and macrophages perhaps function at a later time point, either by amplifying an existing tolerogenic response or by limiting an ongoing inflammation. Lung tissue macrophages transferred to CCR7- mice suggested that a tolerogenic program may be initiated by the macropages, but requires DC migration to the draining lymph nodes where more Treg cells are generated that help in the maintenance of the response [36]. Alternatively, naive T cells recently activated by cDCs, but still undifferentiated may migrate to the lungs and turn into Foxp3+ cells by the signals from the tissue macrophages. Inducible tolerogenic DCs and macrophages may also be generated in the lungs upon low dose chronic exposure to antigens under weak inflammatory signals. The various modes through which epithelial cells of the lungs and airways contribute to tolerance induction are discussed in the previous sections.

The default mucosal tolerance may be switched to inflammatory response under certain situations [1]. This may be required to protect the lungs and airways against invading pathogens. However, frequent or recurrent and strong immune activation may give rise to conditions like asthma and chronic bronchitis. When antigen load in the respiratory tract exceeds a threshold amount, airway and alveolar macrophages may be activated

to secrete pro-inflammatory cytokines. This may trigger a positive feedback loop by suppressing other inhibitory substances like the surfactant. Phagocytic capacity of the AMs may be exhausted in the face of higher antigen load, leading to DC activation and effector T cell generation. Airway epithelial cells are hyper-reactive to certain PRR ligands, such as viral dsRNAs and secrete pro-inflammatory cytokines, although they remain hyporesponsive to LPS and LTA. When pathogen-induced apoptosis of the AECs breaches the barrier integrity, they may directly stimulate the subepithelial APCs, which are no longer tolerized by the epithelium. In addition, necrotic cell death may release alarmins like IL-33 and IL-1α with pro-inflammatory potential. Finally, unfolded protein response (UPR) may be activated by endoplasmic reticulum (ER) stress due to viruses, bacteria, environmental pollutants like cigarette smoke, resulting in pro-inflammatory cytokine secretion from the epithelial cells and induction of apoptosis. Several chronic pulmonary diseases, such as asthma, pulmonary fibrosis and cyctic fibrosis have been linked to the ER stress.

CONCLUDING REMARKS:

The prevalence of lung inflammatory diseases, such as asthma, COPD, pulmonary fibrosis etc has increased over the past 2-3 decades. The clinical efficacy of the latest anti-inflammatory drugs against lung diseases is discouraging, which underscores the necessity to understand the key regulatory mechanisms of immunoregulation in the lung microenvironment. Despite substantial progress been made to explore the basic mechanisms of immune regulation by using in-vitro, ex-vivo and in vivo models, translation of experimental findings to human diseases has remained elusive due to the inherent drawbacks of these models.

Abbreviations : EC - epithelial cell, AEC - airway epithelial cell, cDC - conventional dendritic cell, pDC - plasmacytoid dendritic cell, AM - alveolar macrophage, ALI - acute lung injury, PRR - pattern recognition receptor, TLR - Toll-like receptor, NOD -nucleotide-binding oligomerization domain, RIG-I - retinoic acid-inducible gene 1, Treg - T regulatory.

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