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Lung defences: an overview

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ABSTRACT: Lung defences are dependant on a complex array of mechanisms in the upper airways, which must to be differentiated from those of the distal airways. However, the first lines of defence in the proximal and distal airways are predominantly based on mechanical barriers and several mechanisms related to innate immunity. If pathogens or antigens reach the interstitium, dendritic cells will take up these intruders, reporting antigenic information to the pulmonary lymph nodes, where an adaptive immunity will be generated. Dendritic cells, by doing so, bridge innate immunity with adaptive immunity. Knowledge of these mechanisms is key when modulating immunity to increase defence mechanisms or decrease allergic phenomena.

KEYWORDS: Alveolar macrophages, dendritic cells, lung defences, lung immunity, lymphocytes, neutrophils

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Inspired air is the source of oxygen for the body, but also introduces numerous particles, toxic gases and microorganisms in the airways. The upper and lower airways together represent the largest epithelial surface exposed to the outside environment; the alveolar surface being the size of a tennis court. In order to allow gas exchange, foreign substances and microorganisms must be stopped and removed without undue inflammation.

The upper and lower airways protect the lung with the anatomical barriers. They are associated with the cough reflex and use mucociliary apparatus with enzymes and secretory immunoglobulin A (IgA). The basal layers of the respiratory mucosa in the nose and the conducting airways contain a tight network of dendritic cells (DCs) that sense and catch any invading organisms and bring them to the draining lymph nodes to generate the adaptive immunity. Particles <2 μm reaching the respiratory units beyond the respiratory bronchioles will be caught by alveolar macrophages (AMs) in a milieu that is rich in defence elements, such as IgG, complement, surfactant and fibronectin. Depending on the load of pathogens and the innate immune processes locally involved, various amounts of inflammatory cells, in particular neutrophils, will be rapidly recruited. Once adaptive immunity is also involved, memory T-cells will be found in the interstitium around the bronchi and vessels, as well as in the alveoli (table 1).

THE AIRWAYS AND THEIR MUCOSA

Luminal defence mechanisms

The nasopharyngeal anatomy and airway bifurcation represent important anatomical barriers to prevent the penetration of particles or organisms >2–3 μm into the lower airways. Cough generated by forced expiration allows enough turbulence and shearing forces in the major bronchi and trachea to extrude material such as debris or infected mucus [1]. The mucociliary transport allows impacted particles to be removed from the terminal bronchioles to the trachea by the ciliary beats of epithelial cells in the mucus of bronchi. The airway mucus is composed of the sole phase, a periciliary liquid, ~5–10 μm deep, allowing the cilia to beat and a gel phase on the surface of the cilia of 2–20 μm thickness. The flow of the gel is referred to as mucociliary transport. The physical properties of mucus are provided mainly by mucins, which are mucoglycoproteins and proteoglycans secreted from the surface of epithelial cells and from the glands. Phospholipids are also secreted by the epithelial cells and submucosal glands of the airways, weakening the adhesion of the mucus and altering its physical properties. The mucus gel acts as a barrier for bacteria [2].

Secretory IgAs are released by the epithelial cells as dimeric molecules, associated with a single J chain of 23,000 daltons. IgAs are particularly important as they neutralise toxins and viruses and block the entry of bacteria across the epithelium. IgAs are poor activators of the classical pathway of complement but can activate the alternate pathway, allowing a better opsonisation of bacteria [3].

Lysozyme, lactoferrin or peroxide are carried within the mucus. These substances participate in the nonspecific first-line of defence to invasion by microorganisms. The lysozyme degrades a glycosidic linkage of bacterial membrane peptidoglycans [4]. Epithelial cells, serous cells of submucosal glands, macrophages and neutrophils can be a

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TABLE 1 Major constituents of lung defences

Airways and their mucosa
Luminal defence mechanisms
Anatomical barrier
Cough
Mucociliary clearance
Secretory IgA
Lysozymes, lactoferrins
Defensins
Epithelial cells
Epithelial barrier
Mucin release
Antimicrobial peptides
Bacterial receptors
Chemotactic factors
Growth factors; cytokines
Blood derived cells of the mucosa
Dendritic cells
Lymphocytes (T-cells; γδ; NK cells)
B lymphocytes
Eosinophils; mast cells; basophils
Alveolar spaces
Pneumocyte types I and II
Alveolar macrophages
Lymphocytes
Neutrophils
IgG and opsonins
Surfactant

Ig: immunoglobulin; NK: natural killer.

source of lysozyme. Lactoferrin is an iron-binding protein that reduces the availability of elemental iron, an obligatory co-factor for bacterial replication. Lactoferrin may also be bactericidal by binding to endotoxin [5]. The peroxides from leukocytes (myeloperoxidases) act on thiocyanate ions or produce oxygen radicals that are bacteriostatic or bactericidal. Active plasma components can also extravasate from the blood vessels to the mucosa during airway inflammations. Igs and complement factors then take part in defence mechanisms, as well as in the inflammatory cascade [6].

Epithelial cells

Epithelials provide a mucosal barrier and contribute to the mucociliary clearance function already mentioned. Lining the luminal surface of the airways, they are attached to neighbouring cells by several structures: tight junctions, intermediate junctions, gap junctions and desmosomes [7]. These structures form a barrier between the luminal space and the pulmonary parenchyma. Desmosomes mediate mechanical adhesion of cells to their neighbours and tight junctions completely obliterate the intercellular spaces just below the luminal surface [8]. Transport through gap junctions may be a means for the cells to provide their neighbours with defence molecules, such as antioxidants [9]. This organisation of epithelial cells creates an effective mechanical barrier and allows for polarity in function, thus, maintaining an ionic gradient for bidirectional secretion of many substances.

Epithelial cells recruit inflammatory cells by releasing arachidonic acid derivates [10]; chemokines in response to a variety of stimuli, such as bacterial products, viral infections or cigarette smoke [11–13]. Among the chemokines are interleukin (IL)-8, GRO-α, β, monocyte chemotactic protein-1 or lymphocyte chemoattractant factor (IL-16) [14]. Epithelial cells upregulate adhesion molecules in response to inflammatory stimuli, allowing the adhesion of neutrophils and mononuclear cells to an inflamed area. Epithelial cells can also express major histocompatibility complex of class I and II, when exposed to cytokines such as interferon-γ (IFN-γ). Epithelial cells have then a limited capacity for presenting antigens to lymphocytes and potentially to amplify an antigen-driven lymphocyte response [15]. Normal epithelial cells secrete antimicrobial peptides, such as β-defensins and lactoferrins, which directly contribute to host defence [16].

Blood derived cells of the mucosa

Dendritic cells

DCs lie above and below the basement membrane in a resting or immature state and extend their dendrites between the epithelial cells. They form a network optimally situated to sample inhaled antigens [17, 18]. There are several hundreds DCs per mm^2 in the rat trachea and they become more numerous in response to inhaled antigens [19].

Human lung DCs, like immature DCs derived from blood, are characterised by a high endocytic activity that can be measured with fluorescent isothiocyanate dextran fixation, but show only limited expression of CD40, CD80 and CD86 [20]. Inflammatory stimuli on DCs result in a loss of the antigen capturing machinery and an increase in T-cell stimulatory function, a process referred to as maturation. Once activated, lung DCs migrate to lymphoid structures in the hilar lymph nodes [21]. Using their various pathogen recognition receptors recognising carbohydrate motifs presented on the surface of several microbial organisms, lung DCs continuously report antigenic information from the airways to pulmonary lymph nodes. DCs can even phagocytose apoptotic bodies derived from viral infected epithelial cells. Activated by these bodies and their content they will be able to induce specific cytotoxic T-cells [22]. After antigen uptake, airway DCs migrate to the paracortical T-cell zone of the draining lymph nodes of the lung, where they interact with naive T-cells [23]. Activated CD4 or CD8 memory T-cells will migrate towards other lymphoid structures and nonlymphoid structures of the body, such as the lung [24]. DCs translate their signals from the pulmonary environment into a specific immune response. DCs decrease in number after treatment with glucocortocoids [25], which might help to decrease immune processes. Cigarette smoke also decreases pulmonary DCs and then impacts on the antiviral immune response [26].

T-cells, γδ T-cells, natural killer cells and B lymphocytes

In the absence of inflammation, the epithelium contains few CD4 and CD8 T cells. γδ T-cells and natural killer (NK) cells are part of the innate immunity, independent of DCs. They are likely to play a crucial role in lung immunity, in that they react to pathogens in the absence of preliminary priming. The γδ T-cell clones can also be segregated into T1 or T2, by their cytokine patterns, with a bias toward production of T1

cytokines [27]. NK cells seem not only involved in viral immunity but also in host defence against *Pseudomonas aeruginosa* in acute infections. CD1d restricted NK T-cells were shown to be required for good control of such infections and their activation associated with a rapid pulmonary clearance of these pathogens through enhanced phagocytosis by AMs [28].

In humans, B lymphocytes are scattered in the airways. It is only after recurrent infections that lymphocytes are found in follicles around the airways. These formations are then called bronchus-associated lymphoid tissues.

Eosinophils, mast cells and basophils

Eosinophils, mast cells and basophils are the effector cells of immediate hypersensitivity reactions and allergic diseases. Mature mast cells are found throughout the body, predominantly located near blood vessels, nerves and beneath epithelia. Although normally not present in tissues, basophils are recruited to some inflammatory sites, usually with eosinophils [29]. Eosinophils are abundant in the infiltrates of late phase reactions and contribute to many of the pathological processes in allergic diseases. Cytokines, produced by Th2 cells, promote their recruitment and activation. Eosinophils release numerous mediators that are toxic to parasitic organisms and may injure normal tissues.

IMMUNE RESPONSE IN THE ALVEOLAR SPACES

Alveolar epithelial cells

The importance of type I epithelial cells and their precursors, the type II pneumocytes, will only be briefly mentioned in the current article. However, they are crucial in the homeostasis of the alveoli, for instance in the removal of water and electrolytes. Pneumocytes are also the major source of surfactant proteins (SP). SP A and SP D are members of the collectin family of mamalian lectins that contribute to pulmonary host defences. SPs enhance the phagocytosis and killing of microbes [30].

Alteration of epithelial cells in lung reperfusion injury and in acute respiratory distress syndrome is likely to play an important role in the incidence of pneumonia in these conditions.

Alveolar macrophages

AMs, the resident mononuclear phagocytes of the lung, provide the first line of defence against organisms or particles reaching the lower airways. They must neutralise the invading pathogens or recruit neutrophils and other mononuclear cells. Once the infection or inflammatory process has been controlled, cell debris and exudates must be removed in order to recover the alveolar architecture. The ability of macrophages to interact with pathogens is mediated by surface receptors capable of binding to specific ligands, including toxins, polysaccharides, lipopolysaccharides, complement proteins and Igs.

Toll-like receptors are a family of 11 molecules that initiate intracellular signalling cascades or specific microbial components [31]. Phagocytic cells, such as macrophages, neutrophils and DCs, exhibit the broadest repertoire that results in the activation of several intracellular pathways [32]. The modulation/activation of these receptors may be linked to the capacity of mononuclear cells to release IL-12 instead of IL-10 [33], with a marked influence on lung immunity.

AM will initiate lung inflammation by the release of IL-1α and IL-1β or tumour necrosis factor (TNF)-α, leading to inflammatory cascades in the alveolar milieu, such as the appearance of adhesion molecules on endothelial cells or epithelial cells or the release of chemokines and growth factors. These events are an important part of innate immunity, leading to activation of neighbouring cells, and attract elements from the blood, such as neutrophils.

AM also control inflammation by the release of inhibitors of IL-1 or TNF-α in the form of IL-1 receptor antagonists or TNF-soluble receptors [34]. Macrophages have the capacity to markedly reduce IL-1 or TNF synthesis by their own release of IL-10 [35].

AM have important bactericidal activities realised by the production of lysozymes or defensins, cationic proteins capable of killing a wide variety of bacteria, including mycobacteria or fungi [36]. Reactive oxygen intermediates (superoxide anion, hydrogen peroxide, hydroxyl radicals/or reactive nitrogen) are also involved in killing micro-organisms. Several components of complement are produced by macrophages, as well as the C1q inhibitor [37]. Complement promotes the clearance of immune complex, an important means of eliminating antibody coated bacteria.

AMs can, under circumstances that are currently poorly understood, acquire some characteristics of DCs and may thus be able to activate T-cells [38]. This is in contrast to the popular opinion that they prevent T-cell activation in normal subjects [39, 40]. Thus, macrophages under the influence of innate and adaptive immune mechanisms may change their antigen capacity and/or cytokine production. AMs can indeed produce IL-12 when stimulated by bacterial lipopolysaccharides and IFN-γ or during the interaction of CD40–CD40L on T-cells and macrophages [41].

Lymphocytes

Alveoli contain ~10% lymphocytes of which 50% are CD4, 30% are CD8, 10–15% are killer or NK cells and 5% B lymphocytes. The CD4/CD8 ratio is 1.5, similar to that of peripheral blood. In the alveolar milieu, lymphocytes have a slightly altered phenotype and function related to those of the interstitium. For instance, NK cells in the alveoli have a reduced cytotoxicity compared with interstitial NK cells [42]. B lymphocytes, CD4 and CD8 T-cells are major components of the adaptive immune response and most T-cells have a memory phenotype. Once they are primed, T lymphocytes may be reactivated by DCs around the airways and vessels [43]. The real importance of epithelial cells, endothelial cells or fibroblasts for this purpose mostly relay on *in vitro* studies in which endothelial cells appear potentially the most efficient antigen presenting cell [44]. CD4 and CD8 cells are not only key elements for the defence against viruses but also appear to play a role in bacterial clearance [45].

Neutrophils

The recruitment of neutrophils is a major component of the protective host response to bacterial infections and appears to outweigh the contribution of other immune cells, at least in the acute setting [46]. In the bronchoalveolar (BAL) they normally represent <2% of the cells. However, if AMs in the alveoli

are unable to control infectious agents, a massive flux of neutrophils occurs. Thus, depending on the dose of *Staphylococcus aureus* instilled in the airways, they will later be neutralised by macrophages only or with the influx of neutrophils and with higher doses of the pathogens, the mice will die [47]. Chemotactic factors include C5 fragments generated by the activation of the alternative pathways of complement by bacteria. AMs generate products of arachidonic acid, such as leukotriene B_4. Chemokines are also small polypeptides, critically involved in neutrophil recruitment. The C-X-C chemokines include IL8, GRO-α and GRO-β, found in the BAL of patients with various types of pneumonia [48]. AMs, endothelial cells and epithelial cells have the ability to generate chemokines in response to microbial products or cytokines such as TNF-α or IL-1, as part of the innate immune response.

Activated neutrophils eliminate microorganisms by means of a range of mechanisms, which involve phagocytosis, release of oxygen radicals and production of cytotoxic peptides or proteins. Carbohydrate residues of bacteria are attacked by their enzymes, such as sialidase, x-mannosidase, β-glucuronidase, N-acetyl-β-glucosoaminidase and lysozyme. Cytotoxic protein, such as neutrophil defensins and serine proteinases, damage bacterial membranes [49]. Defects in neutrophil function lead to severe disorders. In Chediak-Higaschi disease, a congenital immunological defect known to be accompanied by severe pyogenic infections, the granules cannot package the protein elastase or the cathepsin-G superfamily [50]. In chronic granulomatous diseases, affected individuals are susceptible to bacterial infections because their phagocytic cells are unable to generate the products of respiratory burst [51]. Neutrophil migration itself is impaired in leukocyte adhesion deficiencies (LAD); thus, in LAD II, a defect in the expression of sialyl Lewis-x, the counter-receptor for E-selectin and P-selectin has been demonstrated [52].

Immunoglobulins and opsonins

Normal bronchoalveolar lavage contains several substances capable of coating bacteria that will enhance phagocytic uptake by AMs, acting as opsonins. Surfactant, fibronectin and C-reactive protein may all have opsonic activities. IgG, which constitutes 5% of the total protein content of BAL [53] is the predominant Ig in the alveoli. IgG_1 and IgG_2 are present in greatest concentration (65% and 28%, respectively), whereas IgG_1 and IgG_3 are considered to be the most important, as only these two antibodies fix complement. IgG_2 is a type-specific antibody against pathogens such as *Streptococcus pneumoniae* or *Haemophilus influenzae* [54]. IgG_4 acts as a reaginic antibody in allergic diseases and increased IgG_4 may lead to hypersensitivity pneumonitis. In the absence of IgG_4, there is a predisposition to sinopulmonary infections and bronchiectasis [55].

Most complement components can be produced *in vitro* by monocytes or macrophages. However, most are produced by the liver and carried to the lung *via* the blood. Activation of the entire complement pathway in the presence of microbes can result in their lysis and killing. When bacteria activate the alternate pathway C3b is released, allowing a good opsonisation of bacteria for neutrophils or macrophages. Complement and, in particular, the alternative complement pathways are likely to play an important role as the first line of defence against many extracellular microbes as part of the innate immune defences [56].

CHANGES INDUCED IN LUNG DEFENCES

The early childhood environment is linked with changes in immune processes and the role of infection in the evolution of immune defences and allergies in children is becoming unravelled. It is increasingly clear that allergies are linked with epithelial changes leading to an increased risk of invasive infections [57]. Various particles and active and passive smoking induce many changes in airway mucosa, leading to chronic bronchitis and acute exacerbations.

Viruses have several strategies to evade lung defences and eventually remain as persistent infections, especially in immunosuppressed patients [58]. Innate and adaptive mechanisms, triggered by viruses and other irritants, may amplify several diseases including asthma.

Immunosuppressants are commonly used either in allergic phenomena, in autoimmune processes, in relation to chemotherapy or after various transplantations. Moderate doses of steroids (>30 mg·day^{-1}) are sufficient to lead to opportunistic infections after a few weeks in adults [59]. Infections related to a wide array of other immunosuppressions have been the subject of an evidence-based review [60]. Common mechanisms involved in the digestive tract and respiratory tract are currently described. It is becoming clear that the immune processes of these two types of mucosa may even influence each other, either *via* innate immunity or adaptive immunity. It is therefore timely to gather this evidence and hope that modulation of immune processes, either through the respiratory or the digestive tract, may become more understood to decrease infections and perhaps reduce allergies. In this review, SCHAAD [61] and SOLÈR [62] discuss the current evidence on how *p.o.* bacterial extracts can decrease the rate and severity of infections in both children and adults with chronic obstructive pulmonary disease.

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