Chapter 2

Pulmonary defence mechanisms and inflammatory pathways in bronchiectasis

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Summary

Over recent years there has been a tremendous increase in the understanding of pulmonary immunity, mostly driven by large research efforts in understanding the basis of asthma and chronic obstructive pulmonary disease. Bronchiectasis is well understood. In this article, an overview of pulmonary defence mechanisms as well as inflammatory mechanisms is given as a basis to understand the pathogenesis of bronchiectasis.

Keywords: Bronchiectasis, inflammatory mechanisms, immunity, pulmonary defence

Bronchiectasis is a chronic disorder characterised by permanent dilatation of the bronchi accompanied by inflammatory changes in their walls and in the adjacent lung parenchyma. The pathogenesis is related to recurrent inflammation of the bronchial walls combined with fibrosis in the surrounding parenchyma. The resultant traction on weakened walls leads to eventual irreversible dilatation [1]. Bronchiectasis can result from defective pulmonary defence mechanisms that lead to recurrent, severe and tissue-damaging microbial insults or chronic bacterial colonisation with persistent inflammation leading to structural changes to the airway wall. Given the fact that restoration of inflammation and return to immune homeostasis is crucial in the lung to protect the delicate gas exchange machinery, it is also possible that bronchiectasis results from defective anti-inflammatory pathways that serve to dampen chronic inflammation. Therefore, in this chapter we provide a brief overview of lung defence mechanisms and how these immune defence mechanisms can contribute to chronic inflammation and structural changes to the airway wall if not properly counter-regulated by anti-inflammatory pathways. The major inflammatory cell types found in bronchiectasis are neutrophils in the airway lumen causing purulent sputum and macrophages, dendritic cells (DCs) and lymphocytes in the airway wall [2, 3].
The latter cells often occur in lymphoid aggregates or so-called tertiary lymphoid follicles, and are typically seen in patients with tubular bronchiectasis and are a major cause of small airway obstruction [4].

**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. Reductions in the cough reflex are associated with increased frequency of respiratory infections, but it is not known at present whether this would also predispose to development of bronchiectasis [5]. The presence of isolated middle lobe bronchiectasis and colonisation with nontuberculous mycobacteria (the so-called Lady Windermere syndrome) has been proposed to be caused by cough suppression [6].

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. Defects in the function of the mucociliary blanket can cause bronchiectasis. The conducting airways are lined with ciliated epithelium and the structure and function of the cilia in propulsing mucus has been extensively studied [7–9]. Genetic defects in the structure of the outer dynein arm proteins that connect microtubules in cilia are the cause of primary ciliary dyskinesia [10]. Other mutations involve the kutu gene, which is involved in the assembly of both the outer dynein and the inner dynein arm [11]. Defects in radial spoke head proteins are associated with abnormalities of the central microtubule pair of the cilium (presence of only one microtubulus rather than two) [10]. Ciliary disturbances (sometimes associated with situs inversus; Kartagener syndrome) almost always lead to bronchiectasis and are often also associated with chronic rhinosinusitis. The correct movement of cilia and function of the mucociliary escalator also depend 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. If the periciliary fluid layer is concentrated (i.e. like in cystic fibrosis (CF)), the periciliary fluid layer becomes thinner and the cilia become entangled in the mucus layer, thus impeding normal ciliary propulsion of the mucus [12, 13].

**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 (PAMPs), which 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 [14]. These molecules can be produced by airway structural cells or by recruited innate immune cells such as neutrophils and macrophages (see later). Lactoferrin chelates Fe$^{2+}$ molecules that are crucial for the growth of some bacteria but also stimulates the function of neutrophils. Lysozyme degrades Gram-positive cell walls. Defensins are made by neutrophils (α-defensins) and epithelial cells (β-defensins). They serve to make pores in bacterial cell walls, and thus are truly antibacterial peptides but also neutralise viruses and fungi and recruit DCs via activation of the CCR6 chemokine receptor on these cells [15]. The proper function of defensins depends on the correct salt concentration in the airway surface liquid [16]. Thus, in CF patients defensin function against *Staphylococcus aureus* is defective, possibly explaining the susceptibility to colonisation, although this theory has also been questioned. LL37 is a well-known airway cathelicidin that is also salt sensitive and has broad antimicrobial activity but
also has effects on innate and adaptive immune cells [17]. Surfactant protein A and D are collectins that opsonise bacteria and viruses such as influenza. A closely related collectin family member is mannose binding lectin (MBL), it is not secreted into the lung lining fluid but is an important circulating factor that can activate the complement cascade. Deficiency of MBL is a cause of recurrent bacterial infections and could be a cause of bronchiectasis. Low MBL levels in CF patients and other forms of bronchiectasis are also associated with a more rapid decline in lung function [18].

**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. 1). Alveolar macrophages serve an important function in the phagocytosis, killing and/or neutralisation 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 alveolocapillary membrane. To avoid collateral damage to type I and type II alveolar epithelial cells (AEC) in response to harmless antigens, they are kept in a quiescent state, producing few inflammatory cytokines [19]. It has been estimated previously, that the pool of alveolar macrophages can handle up to $10^9$

![Figure 1](image.png)

**Figure 1.** When a pathogen enters the lung, it triggers both epithelial cells, macrophages and dendritic cells. The epithelial cells make chemokines that subsequently attract neutrophils that help in phagocytosing the pathogens. All recruited cells together with epithelial cells then make cytokines and growth factors that further enforce innate immune responses to the pathogen by further recruitment of inflammatory cells. TNF: tumour necrosis factor; IL: interleukin; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
intratracheally injected bacteria before there is spill-over of bacteria to DCs and before adaptive immunity is induced [20]. Elegant studies have demonstrated that in vivo elimination of alveolar macrophages using clodronate filled liposomes lead to overt inflammatory reactions to otherwise harmless particulate and soluble antigens [21], but also to an increased sensitivity to bacterial, fungal and viral infection. In their exposed position, alveolar macrophages serve as 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 and lipid mediators; bioactive mediators that recruit other cell types to the lung.

In contrast to alveolar macrophages that reside in the lung and serve as an immediate line of innate defence against inhaled pathogens, neutrophils are recruited within minutes following inoculation of microbes into the lung. The main function of neutrophils is phagocytosis and killing of microbes, particularly fungi such as *Aspergillus* sp. and *Pneumocystis jerovici*. They can also kill microorganisms through the release of α-defensins and lysozyme. Neutrophil killing function depends on oxidative enzymes such as those of the NADPH oxidase system and myeloperoxidase. Chronic granulomatous disease is caused by missense, nonsense, frameshift, splice or deletion mutations in the genes for p22(phox), p40(phox), p47(phox), p67(phox) (autosomal chronic granulomatous disease) or gp91(phox) (X-linked chronic granulomatous disease), which result in variable production of neutrophil-derived reactive oxygen species [22]. Neutrophil extravasation is also a highly organised process requiring the rolling, arrest and diapedesis of cells on the vessel wall. Defects in certain integrins, selectins or their activator can cause defective neutrophil recruitment and cause recurrent pulmonary infections [23]. Once recruited, neutrophils can also further enhance more neutrophil recruitment through production of cytokines (interleukin (IL)-1, tumour necrosis factor (TNF)-α and IL-6) as well as through release of calcium binding proteins of the S100 family (S100A8, A9 and A12) that act on the RAGE (receptor for advanced glycation end products) receptor.

**Induction of innate immune responses in the lung**

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 belong to the family of Toll-like receptors (TLR)1-11, NOD-like receptors, RIG-I-like receptors and C-type lectin receptors [24]. These receptors recognise particular conserved PAMPs on specific groups of microbes. The archetypical TLR4 is expressed at the cell surface and recognises the Gram-negative cell wall component lipopolysaccharide, whereas TLR2 recognises peptidoglycan and TLR5 recognises bacterial flagellin. The endosomal TLR receptors TLR3 recognise double-stranded RNA, TLR7 and TLR8 single-stranded RNA and TLR9 unmethylated CpG motifs [24]. The exact cellular localisation and downstream signalling mechanisms of these pathways have been studied extensively over the past few years and several clinical primary immunodeficiency syndromes have been brought back to deficiencies in one of the signalling intermediates of these pathways.

Deficiency of IRAK4, a critical intermediary in TLR4 signalling causes recurrent bacterial infections, particularly at a young age [25]. Deficiency of the C-type lectin receptor dectin-1 or the downstream signalling intermediate molecule CARD9 causes immunodeficiency to candida and *P. jerovici*, most probably due to reduced induction of T-helper cell (Th)17 responses [26]. Conversely, over activity of these signalling cascades, for example caused by small polymorphisms in or mutations of negative regulators of these pathways are associated with auto-immunity and overzealous inflammatory pathways. As one example, polymorphisms in the ubiquitin editing enzyme TNF-α-induced protein 3 (TNFAIP3, also known as A20), cause hypersensitivity of TLR and cytokine receptors and are often found in patients with systemic lupus erythematosus [27]. Our own unpublished data also show that genetic deficiency of A20 in epithelial cells causes severe mucosal inflammation in response to inhalation of intrinsically harmless proteins, but it is
unknown at present how this could be implicated in the regulation of inflammatory pathways relevant to bronchiectasis.

**Adaptive cellular immunity**

Like innate immunity, adaptive or acquired immunity consists of a cellular and a humoral arm. Cellular adaptive immunity is made up of different types of T-lymphocytes, whereas humoral immunity is made up of B-lymphocytes and plasma cells and their secreted product; immunoglobulins (Ig).

**Induction of adaptive cellular immunity by DCs**

DCs are potent antigen presenting cells that have emerged as key regulators of adaptive immunity (see [28] for a more detailed review on the biology of lung DC function). The general function of lung DCs is to recognise and pick up foreign antigens at the periphery of the body, and subsequently migrate to the draining mediastinal lymph nodes where the antigen is processed into immunogenic peptides and displayed on major histocompatibility complex (MHC)I and MHCII molecules for presentation to naïve T-cells. In fact, these cells should be seen as specialised cells of the mononuclear phagocyte system, which have evolved from the cells of the innate immune system to control adaptive immunity that came later in evolution [29]. DCs express all the pattern recognitions 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. As these cells respond to many noxious stimuli from both the outside world (PAMPs) and from within (danger-associated molecular patterns) and at the same time closely communicate with lung structural cells such as alveolar epithelial cells, 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 [30]. Very recently the first case reports of patients presenting with defects in the DC system have been reported. These DC-deficient patients are at risk of severe viral skin infections and pulmonary infections with atypical mycobacteria, which also leads to bronchiectasis [31, 32]. Our own experiments employing DC-deficient mice have elucidated a crucial role for these cells in the induction of antiviral immunity to influenza virus, via induction of both CD4 and CD8 T-cell responses [33]. Similar conclusions have been reached in models of tuberculosis and bacterial lung infections [34]. 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 chronic obstructive pulmonary disease (COPD) [35]. In humans with bronchiectasis, as well as in a rat model of bronchiectasis, there is an increased infiltration of the airway wall with DCs [2, 3]. The airways of patients with diffuse panbronchiolitis, a disorder of the small bronchioles that can also lead to bronchiectasis, contain increased numbers of DCs that have a clearly activated phenotype, while treatment with neomacrolides reduces the antigen presenting capacities of these DCs [36, 37].

** Constituents of adaptive cellular immunity**

Adaptive cellular immunity consists of defined subsets of CD4+ Th cells and CD8+ cytotoxic 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 (fig. 2). Discrete types of Th cells provide crucial help for different parts of the innate and adaptive immune response [38]. Th1 cells make interferon (IFN)-γ and mainly provide help to monocytic cells, including macrophages and DCs, thus enforcing killing of intracellular pathogens, and at the same time enforcing opsonisation of these through provision of B-cell help. Conversely, Th2 cells make IL-4, IL-5 and IL-13 providing 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 such as fungi. This gap has been breached recently by the discovery of the cytokines IL-17 and IL-22 which are produced by Th17 cells that induce neutrophilic inflammation and production of defensins by epithelial cells and are important for clearance of fungi and extracellular bacteria [39].

The precise signals that induce different types of Th lineage-commitment of naïve T-cells has been intensely studied [38]. Antigen-presenting cells can provide different levels and quality of signal one (peptide-MHC), signal two (co-stimulatory molecules) and signal three (instructive cytokines) to naïve T-lymphocytes upon antigen encounter and triggering of their pattern recognition receptors [29]. When stimulated through the unique T-cell receptor (TCR), naïve CD4+ T-cells differentiate into Th1 cells in the presence of high amounts of IL-12. IL-12 instructs Th1 development via activation of signal transducer and activator of transcription (STAT)4 and the lineage instructing transcription factor T-bet. IL-17 producing cells are induced when exposed to a cocktail of cytokines including transforming growth factor (TGF)-β, IL-6, and IL1α/β, while IL-23 further enhances the proliferation of these cells. The Th17 lineage specific transcription factor RAR-related orphan receptor γt 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 thymic stromal lymphopoietin to activate the transcription factor STAT5 [40–44]. 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 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 co-stimulation offered to naïve T-cells was weak [45–48]. 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, such as natural killer T-cells, eosinophils, mast cells or basophils, that provide IL-4 in trans to activate the Th2-differentiation programme [49]. 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 [50].

Lung DCs are also essential in instructing the selection and expansion of CD8 cytotoxic T-cells that recognise virus-infected cells, cells infected with intracellular bacteria and tumourally

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**Figure 2.** T-cell polarisation induced by dendritic cells (DCs) and their secreted cytokines. When a T-helper cell (Th) type 0 encounters antigen on a DC, it will be induced to differentiate into various mutually exclusive cell fates. Each T-cell differentiation programme is controlled by transcription factors such as Gata-3, forkhead box P3 (Foxp3), RAR-related orphan receptor gamma (RORγ) or T-bet, which enforce Th cell lineage choice. Eventually Th cells emerge that are specialised for performing various antimicrobial tasks. IL: interleukin; Treg: T-regulatory cell; TGF: transforming growth factor; TNF: tumour necrosis factor; IFN: interferon; Ig: immunoglobulin; STAT: signal transducer and activator of transcription.
transformed cells via presentation of endogenous cellular antigen on the MHCI complex [33]. 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 MHCI loading machinery. 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 a FasL- and/or TNF receptor-like apoptosis inducing ligand-dependent manner, causing apoptotic cell death in targets [51].

Several defects in adaptive immunity are associated with increased susceptibility to lung infection and can be an important risk factor for later development of bronchiectasis. Defects in the IL-12/IFNγ/STAT1 axis are a well-known risk factor for mycobacterial infections and invasive Salmonellosis [52]. Defects in the IL-23/Th17 axis are associated with increased risk of fungal infections and P. jiroveci infections [53]. Patients with sporadic or autosomal dominant forms of the hyper IgE syndrome (Job’s syndrome when associated with connective tissue abnormalities) have mutations in STAT3, and hence deficient differentiation of Th17 cells [54, 55]. These patients are at risk for severe recurrent Staphylococcal infections, pneumatoceles and mucocutaneous candidiasis. In recessive forms of the hyper IgE syndrome, mutations in DOCK8 have been described, and these patients are similarly at risk for recurrent sinopulmonary infection and have defects in Th17 generation [56]. The few biopsy studies that have been performed in bronchiectasis have seen increased infiltration of the bronchial wall with CD4 and CD8 T-cells. The neutrophilic inflammation seen in CF and other forms of bronchiectasis is typically associated with the increased presence of Th17 cells [57]. In bronchiectasis associated with allergic bronchopulmonary aspergillosis, one has also observed increased numbers of Th2 cells, thus explaining the association with sputum eosinophilia.

**Humoral immune mechanisms in the lung**

Humoral immunity plays a predominant role in protection from severe infections with encapsulated bacterial strains. Antibodies are well known for their neutralising 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 (so-called natural antibodies), also have the capacity to activate complement and opsonise bacterial cell walls and capsules, thus facilitating clearance of the pathogens. 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. Maybe the most prevalent cause of bronchiectasis is deficiencies in humoral immunity, such as common variable immunodeficiency (CVID), a group of disorders characterised by low to absent Ig and various degrees of T-lymphocyte abnormalities [18, 58]. CVID can be caused by mutations in the proteins involved in T–B-cell communication such as ICOS, BAFF, TACI and APRIL [59, 60]. This is a rapidly evolving field and it is only a matter of time before all these mutations can be diagnosed on a routine basis.

**Organised lymphoid structures and bronchiectasis**

The organised accumulation of lymphocytes in lymphoid organs serves to optimise both homeostatic immune surveillance, as well as chronic responses to pathogenic stimuli [61]. During embryonic development, circulating haemopoietic cells gather at predetermined sites throughout the body, where they are subsequently arranged in T- and B-cell specific areas, leading to the formation of secondary lymphoid organs, such as lymph nodes and spleen. In contrast, the body has a limited second set of selected sites that support neo-formation of organised lymphoid aggregates in adult life. However, these are only revealed at times of local, chronic inflammation when so-called tertiary lymphoid organs (TLO) appear. Just like in lymph nodes and spleen, areas of TLO are characterised by formation of specialised high endothelial venules and the organised
production of chemokines leads to cellular organisation of T-cells and B-cells in discrete areas. In humans, TLO has been observed in the joint and lung of rheumatoid arthritis [62], around the airways of COPD patients [63] and in the thyroid [64]. Certain infectious diseases are also accompanied by the formation of TLO. Influenza virus infection of the respiratory tract leads to formation of inducible bronchus-associated lymphoid tissue (iBALT) that supports T- and B-cell proliferation and productive Ig class switching in germinal centres [65, 66]. Tertiary lymphoid follicles or iBALT is frequently seen in tubular bronchiectasis, and the close association with bronchi might explain the obstruction of small bronchioles and airway obstruction that is often seen. This is certainly the case in rheumatoid arthritis-associated bronchiectasis, in which bronchial obstruction is often caused by strongly enlarged TLOs that impinge on the lumen of the airway, an entity known as follicular bronchiolitis by pathologists and reflecting the presence of B-cell follicles inside TLO structures [62]. Formation of TLO could be the result of chronic colonisation of bronchiectatic Airways by microbes, and indeed it has been proposed that latent adenoviral infection is a cause of follicular bronchiectasis [4]. 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 of the disease. In TLO associated with rheumatoid arthritis-bronchiectasis, one has indeed seen the production of pathogenic antibodies to citrullinated proteins [62].

Anti-inflammatory 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 oedema, inflammation and cellular recruitment will lead to thickening of the alveolar wall and will jeopardise 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. Even following 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 such as bronchiectasis. 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 [67]. When mixed with DCs in vitro, alveolar macrophages suppress T-cell activation through the release of nitric oxide (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 (Treg). Natural Tregs express high levels of CD25 and express the lineage specific transcription factor Foxp3 [68]. 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 [69]. 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 [70]. As bronchiectasis is a disorder of chronic inflammation accompanied by microbial colonisation, it is very likely that increased Tregs are found inside lesions, although this has not been formally addressed. It is also possible that failure of Treg function at a certain stage of the disease contributes to ongoing inflammation, which might ultimately progress to fibrosis. In this regard it is a striking observation that Tregs also make TGF-β as part of their suppressive programme. TGF-β might be at the crossroads of immunoregulation and fibrosis initiation.
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 recognised or not [71]. Epithelial cells express many pattern recognition receptors and the sensitivity of these can be regulated through negative regulators of signalling. Finally, some epithelial derived cytokines, such as IL-37, have an intrinsically anti-inflammatory effect on innate immunity in the lung [72]. It is currently unknown if defects in these counter-regulatory mechanisms are involved in the maintenance of inflammation in patients with bronchiectasis.

**Conclusion**

There has been great progress in our knowledge of innate and adaptive immune responses in the lung. Immune defects in innate and adaptive cellular and humoral immunity can all lead to bronchiectasis. In contrast to other obstructive airway diseases, such as asthma and COPD, we have not yet fully grasped the immunopathogenesis of chronic inflammation in this disorder.

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**Statement of interest**

None declared.

**References**


