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REVIEW

Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms

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ABSTRACT: Bronchiectasis is a chronic and debilitating lung disease, characterised by irreversible dilatation of the bronchi as consequence of airway injury and remodelling due to recurrent or chronic airway inflammation and infection. The underlying aetiologies include autoimmune diseases, severe infections, genetic abnormalities and acquired disorders.

The pathogenesis of bronchiectasis is poorly understood. Three distinct pathogenetic elements, namely infection, inflammation and enzymatic actions, which interact with each other, have been implicated in the pathophysiology of bronchiectasis.

Some recent observations indicate that airway inflammation in bronchiectasis comes from a deregulated cytokine network independent of bacterial airway colonisation.

In the present review, current knowledge about cellular and molecular inflammatory events in the dynamic process of host–pathogen interaction that are thought to play a relevant role in the pathogenic mechanisms of airway wall destruction leading to bronchiectasis are discussed.

KEYWORDS: Airway infection, airway inflammation, bronchiectasis

Bronchiectasis is a pathological description of a progressive and debilitating disease in which airways become permanently dilated as the result of inflammatory-related destruction of structural components of the bronchial wall [1, 2]. In general, as shown in table 1, bronchiectasis represents the end stage of several pathological processes, ranging from foreign body obstruction to post-infectious damage, genetic defects, altered host defence and autoimmune disease [3]. However, the underlying cause may be impossible to identify in about 50% of cases [4].

The disease can manifest itself in either of two forms: limited to one area (localised) or more widespread (generalised) and often accompanied by rhinosinusitis and diffuse airflow obstruction [2]. The clinical course is characterised by a persistent or recurrent cough, purulent sputum production, occasional haemoptysis, recurrent exacerbations, fatigue and shortness of breath [1].

Although patients with idiopathic bronchiectasis have early onset disease, nowadays the age of onset has become later due to improved sanitation, introduction of childhood immunisation and the early and frequent use of antibiotics.

The clinical spectrum of the disease is broad. A small subset of patients, for reasons that are unknown, develops early onset and rapidly progressive disease. Another subset of patients, that constitutes the vast majority, appear to deteriorate slowly over decades from an increase in exacerbation frequency, sputum volume and extent of bronchiectasis. Finally, some patients, usually those with single lobe involvement, can be asymptomatic between exacerbations and not deteriorate even after decades [5].

The quality of life of affected subjects is often severely impaired and, due to frequent admissions to hospital, the socioeconomic cost of the disease is high [6].

The pathogenetic mechanism leading to bronchiectasis is complex and, to date, not well understood. The current point of view considers that an exaggerated and uncontrolled neutrophilic airway inflammatory response triggered by bacterial infection of the lower respiratory tract is the first step in the pathogenetic mechanism leading

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to bronchiectasis [7–9]. Based on this view, airways are progressively damaged as the result of the interplay between microbial infection, airway inflammation and tissue-damaging substances secreted by neutrophils [9–11].

Some observations indicate that airway inflammation in bronchiectasis comes from a deregulated cytokine network [12–14], independent of bacterial airway infection. In the early phases of both cystic fibrosis [12, 15–17] and bronchiectasis [14], active airway inflammation has been reported even in the absence of microbial infection.

AIRWAY INFLAMMATION AND INFECTION

Knowledge about airway inflammation in chronic airway inflammatory disorders has increased considerably in recent years, thanks to the application of methods such as bronchoalveolar lavage (BAL), bronchial biopsy and, more recently, induced sputum [18, 19]. However, despite considerable progress being made in the understanding of airway inflammation in asthma and chronic obstructive pulmonary disease (COPD), little is known of this in bronchiectasis [20].

Host defence and inflammatory response are based on a complex cytokine network that leads to the activation and expansion of cells involved in the immune response [21]. Severity of inflammatory response depends on the interplay between pro-inflammatory cytokines, which are upregulated, and anti-inflammatory cytokines and various cytokine inhibitors, which are released to limit its extent and duration [22]. So, pro-inflammatory cytokines released in response to injury or infection when not adequately counterbalanced by anti-inflammatory cytokines cause a local or systemic pathology [21].

In idiopathic bronchiectasis, chronic bronchial infection and inflammation interacting with each other are responsible for progressive lung damage [23].

The kinetics of the establishment of infection and their relationship with the subsequent inflammatory response are poorly understood [24]. Generally, airway inflammation has been considered a consequence of airway infection rather than a prelude to it [15].

An abnormal cytokine network and/or uncontrolled activation of effector cells can manifest itself as inflammation independent of infection and/or inflammation disproportionately increased or prolonged in relation to the level of bacterial stimuli [25]. Recent evidence suggests that in bronchiectasis, airway inflammatory response triggered by bacterial stimulation is excessive in relation to the bacterial burden, and continues to reverberate even after the infection is controlled [26]. The altered homeostasis of airway inflammatory response to bacterial infection in the dynamic process of host–pathogen interaction dictates the clinical manifestations of the lung disease.

Commonly, bronchiectasis airways are infected by bacteria such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* [27, 28].

Pseudomonas aeruginosa *infection*

P. aeruginosa is an opportunistic pathogen rapidly cleared from airways of healthy subjects [29]. In cystic fibrosis and bronchiectasis subjects it is responsible for chronic infection [23].

TABLE 1 Disorders predisposing to bronchiectasis

Airway obstruction	Foreign body
	Tumour
	Broncholithiasis
	External compression of bronchus
Cystic fibrosis	
Reduced host immunity	Congenital and acquired hypogammaglobulinaemia
	Malignancy
	HIV infection
Post-infection (tuberculosis, pertussis, measles, *etc.*)	
Allergic bronchopulmonary mycoses	
Chronic *Mycobacterium avium* complex infection	
Aspiration or toxic inhalation	
Rheumatoid arthritis	
Systemic lupus erythematosus	
Relapsing polychondritis	
Sjögren syndrome	
Inflammatory bowel disease	
Other congenital disorders	α_1-Antitrypsin deficiency
	Primary ciliary dyskinesia
	Tracheobronchomegaly (Mounier-Kuhn syndrome)
	Bronchial cartilage deficiency (Williams–Campbell syndrome)
	Young's syndrome (azoospermia and chronic sinopulmonary infections)
	Bronchopulmonary sequestration
	Marfan syndrome
Yellow nail syndrome (lymphoedema, pleural effusions, hypertrophic nails)	

The virulence of *P. aeruginosa* is multifactorial, including several cell-associated and secreted proteins such as elastase A, phospholipase C, and those translocated through the type III secretion system [30].

LAPA E SILVA *et al.* [31] have suggested that *P. aeruginosa* infection, through a cell-mediated immune reaction, has an important role in the pathogenetic mechanism of bronchiectasis.

Alveolar macrophages (AMs) and epithelial cells are a major first line of defence following *P. aeruginosa* lung infection [32, 33]. Stimulated AMs, secreting a number of pro-inflammatory cytokines and chemokines, play a direct role in the recruitment of neutrophils [26, 34].

Activated neutrophils, as indicated by some studies in patients with cystic fibrosis, have been implicated in the induction of a mutation in *P. aeruginosa* leading to alginate production and biofilm formation [35] that protects bacteria from activated neutrophils [36, 37]. The mucoid *P. aeruginosa* biofilms withstand opsonisation and phagocytosis by cells of the immune system [38–40], as well as demonstrating an increased tolerance to toxic oxygen radicals [35, 41] and antibiotics [42]. As a consequence of this mutation, patients develop a vigorous and persistent neutrophilic inflammatory response. Although the change from nonmucoid to mucoid phenotype is more relevant in cystic fibrosis, it is also found in severe bronchiectasis and settles patients into a vicious cycle of airway obstruction, infection and excess inflammation, which results in lung destruction and further damage to the clearance processes [26].

There is accumulating evidence involving natural killer (NK) cells in *P. aeruginosa* lung infection. Phenotypic differences in NK cells have been shown in mouse strains susceptible and resistant to chronic lung infection with *P. aeruginosa* [43].

NK cells accumulate early in lung parenchyma during inflammation, recruiting other cell types, including neutrophils and T-cells [44, 45].

Mycobacterium avium *complex infection*

Mycobacterium avium complex (MAC) is ubiquitous in the environment and, normally, nonpathogenic in healthy subjects [46, 47].

MAC infection can cause bronchiectasis and bronchiolectasis [48, 49] in subjects who show no signs of systemic immunological diseases [49–51]. Most of these patients are middle-aged nonsmoking females and have characteristic computed tomographic findings of peripheral nodules and bronchiectasis [52, 53].

Pathologically, MAC lung infection is characterised by extensive granuloma that affect the airways causing airway narrowing and destruction of the airway muscle layer, and can lead to bronchiectasis [49].

In the specific immune response to MAC infection, CD4-positive T-cells have a major role [54, 55]. In addition, NK cells participate in the innate immune response against this pathogen [55–57].

Some observations, both *in vitro* and *in vivo*, suggest that specific cytokines and their interplay can confer protection or susceptibility to MAC infection. Tumour necrosis factor (TNF)-α and interferon (IFN)-γ are essential for the development of protective immunity against tuberculosis and MAC in mice [46, 54]. Mice lacking IFN-γ or interleukin (IL)-12, a major stimulus for IFN-γ production, have increased susceptibility to *Mycobacterium tuberculosis* [46, 58, 59] and to MAC [46, 60].

Subjects with genetic deficiencies in IFN-γ protein or receptor have increased susceptibility to mycobacterial infection [46, 61]. Several families are reported to be vulnerable to disseminated MAC disease, and their immunocompromise is caused by the decrease in IFN-γ production [62, 63] or by IFN-γ receptor abnormality [64].

Haemophilus influenzae *infection*

KING *et al.* [27] have reported that subjects with bronchiectasis and recurrent infections with nontypeable *Haemophilus influenzae* (NHTi) present a type 2 T-helper cell (Th2) predominant response with production of IL-4 and IL-10. Conversely, cytokine pattern in control subjects was consistent with a Th1 response. Therefore, it has been suggested that a nonclearing adaptive immune response to chronic infection of the lower respiratory tract in bronchiectasis subjects contributes to the airway inflammatory process [27].

Recently, it has been reported *in vivo* that NHTi form adherent biofilms on the apical surface of airway epithelium [65]. The epithelium in turn responds through increased secretion of several innate and adaptive immune factors that mediate airway inflammation [65]. *H. influenzae* stimulates respiratory epithelial production of macrophage inflammatory proteins, IL-8 and TNF-α both *in vitro* [66] and *in vivo* [67].

It is also suggested that *H. influenzae* causing airway inflammation can act as a gateway organism, paving the way for colonisation with *P. aeruginosa* [68].

THE ROLE OF CELLS IN BRONCHIECTASIS AIRWAY INFLAMMATION

Neutrophils

Neutrophils play the most relevant role in innate immune responses [69, 70]. They rapidly migrate into the inflamed tissues and are provided by potent effector mechanisms such as phagocytosis, production of reactive oxygen mediators and antimicrobial substances [70, 71].

Neutrophils are the predominant cells present in both sputum and BAL fluid of bronchiectasis subjects [72, 73]. Airway neutrophils are increased in clinically stable bronchiectasis subjects, including those with sterile bronchi, but their numbers further increase when airways are colonised by microorganisms with potential pathogenicity [13].

On bronchial biopsy, high neutrophil densities have been reported in the lamina propria of bronchial mucosa [74, 75].

Neutrophil recruitment to the airways involves a number of pro-inflammatory mediators, including IL-1β, IL-8, TNF-α and leukotriene (LT)B_4 [9, 10, 13, 76, 77].

Transepithelial migration of neutrophils from the intravascular compartment to the sites of inflammation is a regulated multistep process involving a series of coordinated interactions between adhesion molecules expressed on the surface of endothelial cells and their counterparts on leukocytes [78–83].

Three families of adhesion molecules mediate this process: the selectins; the integrins CD11/CD18; and the immunoglobulin super-family, including intercellular adhesion molecule (ICAM)-1, vascular adhesion molecule (VCAM)-1 [80, 83–85] and CD47 [86].

These adhesion molecules are upregulated by IL-1, TNF-α, lipopolysaccharides [84, 85, 87] and IL-8 [88], all of which are abundant in the airways of subjects with bronchiectasis [8, 9, 72, 74, 89].

ZHENG *et al*. [85] have reported that serum levels of E-selectin, ICAM-1 and VCAM-1 were significantly higher in bronchiectasis with regard to control subjects. Interestingly, serum levels of adhesion molecules correlated with functional parameters and sputum volume production suggesting that adhesion molecules take a relevant place in the sequence of the events leading to bronchiectasis [85].

Recently, evidence has been accumulating that Toll-like receptors (TLRs) are modulators of neutrophil–epithelial cell interaction [78]. TLRs recognise specific pathogen–associate molecular patterns and are expressed by most immune cells, including neutrophils and epithelial cells [90]. When TLRs encounter specific pathogen–associate structures, they trigger a signalling cascade that leads to the activation of nuclear factor (NF)-κB and other transcription factors [91].

Exposure of neutrophils to TLR agonists causes production of IL-8, shedding of L-selectin from the cell surface, upregulation of CD11b/CD18, production of superoxide, and an increase in the rate of phagocytosis [90].

Increased mRNA levels of TLR2 has been reported on sputum supernatant of subjects with bronchiectasis [92].

Adherent neutrophils finally migrate into the airways under the direction of neutrophil chemotractant factors such as IL-8, LTB_4 [93–95] and TLR4 agonists [96].

When activated, neutrophils secrete a number of proteases, including neutrophil elastase (NE), catepsin G and proteinase-3 [95].

NE has proteolytic effects and induces the release of cytokines, such as IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor [97, 98]. It is also a powerful segretagogue, inducing the expression of the mucin gene MUC5AC *via* the generation of intracellular reactive oxygen species (ROS) [99].

In steady state bronchiectasis, sputum NE levels correlate with the percentage of neutrophils, pro-inflammatory cytokines (IL-8 and TNF-α) and 24-h sputum volume that is a marker of disease activity [8].

Upon stimulation (TNF-α and IL-1β) neutrophils also release matrix metalloproteinases (MMPs) [100–102]. Increased levels of MMP-8 and MMP-9 have been reported in BAL fluid of subjects with bronchiectasis [103, 104]. MMP-8 and MMP-9 expression in the bronchiectasis airways correlate significantly with airway neutrophil numbers but not with lung function and extension of disease [105].

Neutrophil toxic products impair the structure and functioning of the airway mucosa by digesting airway elastin, basement membrane collagen and proteoglycan, contributing in this way to the progression of the disease (fig. 1) [8, 99, 105–112].

Macrophages

The role of macrophages in bronchiectasis is less well defined than that of neutrophils. In bronchial biopsies from bronchiectasis subjects, higher densities of macrophages have been found throughout the entire lamina propria compared with normal controls [74].

A significantly higher number of macrophages has been reported in bronchiectasis subjects with regular sputum production compared with nonproducers, suggesting that airway macrophages could be related to disease activity [74].

Macrophages contribute to neutrophil influx into the airways *via* the production of TNF-α [75] and endothelin (ET)-1 [113]. They also function as regulatory cells, releasing a number of inflammatory mediators, including TNF-α, IL-8, other CXC chemokines, monocyte chemotactic peptide 1, LTB_4, ROS and a number of elastolytic enzymes [95, 114, 115].

VANDIVIER *et al*. [98] have reported that patients with bronchiectasis had higher levels of apoptotic neutrophils than patients with chronic bronchitis.

Apoptotic cells target themselves for recognition and uptake into phagocyte-expressing surface ligands, in particular phosphatidylserine (PS), which interacts with specific receptors on the macrophages surface [98, 116–118].

PS receptor possesses potential elastase cleavage sites that would result in loss of the putative PS-binding region of the molecule [98, 119]. It has been reported that NE can cleave the PS receptor on phagocytes, impairing apoptotic cell clearance, contributing in this way to ongoing bronchiectasis airway inflammation [98].

Abnormal accumulation of apoptotic cells results in chronic tissue damage and persistent inflammation [98, 120]. Indeed, apoptosis of dying inflammatory cells is an integral step in the ending of inflammatory response, and failure of this process may have detrimental effects on airways [98, 121].

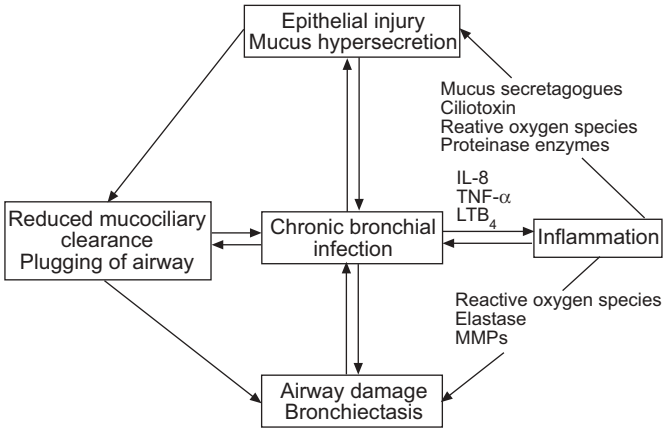

FIGURE 1. Schematic representation of a vicious circle of events which occurs during chronic bronchial infection. IL: interleukin; TNF: tumour necrosis factor; LT: leukotriene; MMP: matrix metalloproteinase.

Lymphocytes

In both experimental model [31] and human bronchiectasis [122] T-lymphocytes infiltrate airways. Infiltrating T-cells have been observed, predominantly in the lamina propria, but also dispersed in the epithelium. T-cells are arranged just below the basement membrane of the epithelium, sometimes isolated but usually packed in clusters of cells [122].

Results of available studies on the CD4+/CD8+ ratio have yielded conflicting results. In one study, CD4+ cells were prevalent, with the CD4+/CD8+ ratio being 3:1 in bronchiectasis subjects *versus* 1.3:1 in control subjects [110]. In another study on BAL fluid, CD4+ and CD8+ cells assessed by flow cytometry were reported in equal numbers [111].

ELLER *et al.* [72] found that CD8+ cells were predominant in two thirds of patients on bronchial biopsy from 22 subjects with bronchiectasis of diverse aetiology. In the remaining biopsy sections, CD4+ cells were predominant and these were mainly clustered in follicle-like structures [72]. Other studies have reported a predominance of CD8+ T-cells [31, 122]. However, more recent studies have shown that bronchiectasis may be characterised by either increased CD4+ or CD8+ T-cells [72] or, indeed, no predominance of either phenotype [111].

The available data suggest that an ongoing cell-mediated immune response contributes to the inflammatory process observed in bronchiectasis [31, 75, 122].

The importance of cytotoxic T-cells is supported by some observations in subjects with one type of ''bare lymphocyte syndrome'' who lack transporter associated with antigen presentation (TAP) and cannot put major histocompatibility complex (MHC) class I molecules on their surface. In these patients, CD8+ T-cells are lacking, because they cannot be positively selected in the thymus, which lacks MHC class I expression. Without expression of MHC class I and CD8+ T-cells, these patients suffer from persistent respiratory viral and bacterial infections. A consequence of these repeated respiratory infections is the development of anatomic damage to the airways that, ultimately, results in bronchiectasis [123–125].

NK cells have been implicated in the development of familial bronchiectasis in subjects with TAP gene mutation which, impairing Class I molecule expression, results in NK cell dysfunction [123]. The role of NK cells in bronchiectasis has recently received support from the work of BOYTON *et al.* [126], who have reported that subjects with human leukocyte antigen (HLA)-c group 1 homozygosity are genetically susceptible to bronchiectasis. HLA-c group 1 homozygosity and the interplay between HLA-c/KIR genes causes excessive or inappropriate activation of NK cells, suggesting a role of these cells in the pathogenetic mechanisms of the disease [126].

Eosinophils

The role of eosinophils in the pathogenetic mechanism of bronchiectasis is, at the moment, unknown. In bronchiectasis, an increased number of EG2+ eosinophils in the bronchial mucosa has been reported, although their number was smaller than neutrophil, macrophage and T-cell numbers [75]. An increased number of eosinophils has also been observed in the sputum of patients with bronchiectasis [127].

In adult subjects with idiopathic bronchiectasis, serum eosinophilic cationic protein (ECP) levels have been reported to be significantly increased compared with sex- and age-matched controls and COPD patients. In contrast, blood eosinophil counts were not increased compared with normal controls or patients with COPD [128].

Airway eosinophil activation is a feature of COPD exacerbations and is linked to disease severity [129].

The clinical and pathological significance of increased airway eosinophil infiltration and serum ECP levels in bronchiectasis subjects are, at the moment, not known, but it is possible that recruitment of eosinophils in the bronchiectasis airway is related to disease severity.

Epithelial cells

Until recently, the respiratory epithelium has been considered as a physicochemical barrier provided by several constitutive innate mechanisms (*e.g.* mucociliary clearance, antibacterial molecules, resident macrophages and lymphocytes) that constantly defend airways from harmful inhaled irritants, viruses and bacteria [130, 131].

There is increasing evidence that airway epithelium actively participates in the pathophysiological mechanisms of respiratory disease [132]. Bronchial epithelial cells synthesise and release a number of pro-inflammatory factors, both constitutively and in response to external stimuli [133], providing a local mechanism to induce, amplify or modulate ongoing inflammation [132].

Human bronchial epithelial cells, when exposed to bacterial endotoxin, markedly increase the expression and/or release of pro-inflammatory mediators, including IL-8 and TNF-α, which have a pivotal role in migration and activation of neutrophils to sites of inflammation [77, 133].

Human airway epithelial cells produce ET-1, which promotes neutrophil adhesion to endothelial cells, migration to areas of inflammation and the release of elastase *in vitro* [113].

Bronchial epithelial cells express ICAM-1 both directly by epithelial cell interaction with bacteria and/or indirectly by epithelial cell communication with other cell types through cytokines [134]. Airway response to bacterial pathogens is modulated by increased expression of ICAM-1 [66, 134]. Interaction of ICAM-1 with CD11/CD18 on leukocytes is determinant for leukocyte adhesion to airway epithelial cells [90, 135] and decreased ICAM-1 expression or function may result in impaired leukocyte recruitment and/or antimicrobial activity [134, 136, 137].

Therefore, the current evidence suggests that airway epithelial cells are key orchestrators of inflammatory response through the release of both pro-inflammatory cytokines and the upregulation of ICAM-1 adhesion molecules.

Epithelial cells express TLRs that, when activated, through NF-κB and other signalling molecules, result in transcriptional upregulation of inflammatory mediators [138]. TLRs can also be activated by host-derived molecules and membrane lipids produced as a result of tissue damage [139]. Epithelial cells have many of the cell surface molecules associated with

antigen presentation, including MHC class I and MHC class II and CD40 [138]. In an experimental rat model of bronchiectasis it has been observed that epithelial cells express MHC class II molecules [31]. It is of interest that emergence of class II MHC antigen in epithelial cells was correlated to the histological severity of bronchiectatic changes [31].

OXIDATIVE STRESS

Oxidative stress indicates all the functional or structural alterations caused by ROS [140–142]. Normally, toxicity of oxidants and the protective antioxidant defence system are well balanced [143]. During the respiratory burst the excessive quantities of free radicals produced by inflammatory cells overwhelm host antioxidant defences causing severe damage to the airway epithelial cells and other airway structures [144, 145]. However, ROS can exacerbate inflammation, inducing cytokine and chemokine production through stimulation of inflammatory genes controlled by NF-κB [146].

Oxidative stress is believed to play an important role in the pathophysiology of bronchiectasis and other chronic inflammatory respiratory disease such as asthma and COPD [142, 147, 148].

Activation of neutrophils, eosinophils and macrophages induces a respiratory burst resulting in marked production of superoxide anion, which then undergoes spontaneous or enzyme-catalysed dismutation to form hydrogen peroxide (H_2O_2) [144].

Increased levels of exhaled H_2O_2 have been reported in bronchiectasis subjects [140]. Interestingly, exhaled H_2O_2 levels significantly correlated with neutrophil differential counts in induced sputum, extent of disease, lung function impairment and disease severity [73].

Neutrophil is an endogenous source of oxidants [73, 140] and, recently, it has come to light that TNF-α induces neutrophil release of H_2O_2 *in vitro* [149]. This means that the high concentrations of this cytokine observed in bronchiectasis may trigger a prolonged neutrophil release of H_2O_2 [140]. Bacterial infections may contribute to oxidative stress by facilitating the recruitment and activation of phagocytic cells in the lung [150]. Indeed, bronchiectasis subjects with *P. aeruginosa* infection present significantly higher levels of H_2O_2 compared with bronchiectasis subjects without *P. aeruginosa* infection [73].

Oxidants damage lipids (lipid peroxidation) leading to the production of isoprostanes, of which 8-iso-prostaglandin F_2 (8-iso-PGF_2) is the best-characterised isomer. High concentrations of induced sputum 8-iso-PGF_2 have been reported in subjects with bronchiectasis and asthma [151, 152].

The levels of oxidative stress indicators, such as H_2O_2 or 8-isoprostane, in exhaled breath condensate have been shown to reflect the intensity of the underlying inflammation in bronchiectasis [140], asthma [152] and COPD [153].

There are various mechanisms which protect against oxidative stress. One of these is the induction of a stress-response protein, haem oxygenase (HO) [142, 154]. HO-1, an inducible form of HO, catalyses the degradation of haem to bilirubin, producing free iron and carbon monoxide [155]. A number of cytokines and oxidants, including ILs, TNF-α, IFN-γ, H_2O_2 and nitric oxide are capable of inducing HO-1 [77, 154, 156]. The induction of HO-1 has been shown to be involved in the resolving of acute inflammation under experimental conditions and it has been suggested that it may play a cytoprotective role in haem and oxidant-induced cellular insults [141, 157].

Increased levels of exhaled carbon monoxide have been reported in patients with bronchiectasis as a reflection of increased oxidative stress and consequent HO-1 activation [145].

CONCLUSION

In the present review, some aspects of mucosal airway inflammatory events in bronchiectasis are briefly covered. The emerging conclusion is that airway bronchiectasis alterations, independent of triggering causes, came from the uncontrolled recruitment and activation of a number of inflammatory cells. The contribution and sequential role of each inflammatory cell implicated in producing the typical pathology of bronchiectasis are still poorly understood.

There are data suggesting that bronchiectasis airway inflammation results from a deregulation of the innate, but also adaptive, immune responses in the context of chronic airway bacterial infection.

It is possible that uncontrolled neutrophil influxes and their activation into the airways is the result of persistent activation of effector mechanisms of innate immunity. In the near future, more research is required to better understand the signalling mechanisms for innate immune responses and the nature of any deficiencies in innate immunity associated with bronchiectasis. The capacity of cytokines to precisely control the movement of inflammatory cells into inflamed airways suggests that cytokines and their receptors might provide targets for therapeutic treatment to modulate airway inflammation, in order to prevent further deterioration in lung function and to better control symptoms.

A number of important questions remain unresolved and deserve further investigation. The presumed triggering events of bronchiectasis are more common than bronchiectasis itself. It is important to understand why some individuals exposed to a triggering event develop permanent damage leading to bronchiectasis while others do not. Similarly, identification of risk factors related to disease progression, particularly in children, is of particular clinical importance since this can allow for early intervention and so minimise long-term morbidity and mortality.

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