The immunology of bronchiectasis – complex machinery unravelled

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ABSTRACT

Bronchiectasis is a complex process of irreversible dilatation of the bronchi and bronchioles with associated structural damage to surrounding lung tissue. It has many causes including cystic fibrosis, primary ciliary dyskinesia, primary and secondary immune deficiency. The pathophysiological insult is dependent on the underlying cause but involves both the innate and adaptive immune systems. Interaction of these systems and a thorough understanding of the processes involved may uncover new diagnostic and therapeutic strategies.

INTRODUCTION

Bronchiectasis is a chronic pulmonary disorder that is characterised by irreversible dilatation of the bronchi and bronchioles with associated structural damage to surrounding lung tissue. This results in excessive mucus production, chronic cough, airflow limitation, poor quality of life and eventual demise if the condition remains unchecked.[1] Bronchiectasis is currently regarded as an orphan lung disease as there is a lack of research in this area.[2,3] This is due to significant decline in the prevalence of this condition in developed countries especially in the paediatric population.[4] There is current evidence of increasing rates of bronchiectasis particularly in adults.[5] Some authors attribute this 'rise' in incidence to the increased use of high-resolution CT-scanning (Fig. 1), which can detect very early changes in the lungs (Table I).[5] The hallmark of this disease is occurrence of pulmonary exacerbations, which lead to lung function decline.

Table I. High-resolution computed tomographic (CT) features of bronchiectasis

Signet ring sign: internal diameter of the bronchi larger than accompanying vessel

- Bronchial dilatation
- Failure of tapering of the bronchi
- Presence of peripheral airways at the CT periphery
- Bronchial wall thickening with mucous plugging or impaction with tree-in-bud pattern
- Mosaic perfusion
- Air trapping on expiratory films

The human airway is continuously exposed to airborne pathogens, which are cleared by interactive processes, involving both the innate and adaptive immune systems, in the lung. Bronchiectasis is thought to occur as a result of deregulation of the innate and adaptive immune systems, with uncontrolled recruitment and activation of inflammatory cells in the airway.[6] This leads to the destruction of normal lung architecture and a variety of immune deficits in the region of the damaged airway.[7]

The immunology of bronchiectasis involves the complex interplay between infecting pathogens and the immune responses, which are thought to be abnormal in bronchiectasis. There are numerous duplications and redundant activities in the immune system, which form part of a complex machinery that protects against pathogenic invasion. This review focuses on the role of the immunology of bronchiectasis with emphasis on the innate and adaptive immune systems.

PATHOGENESIS OF BRONCHIECTASIS

The exact pathophysiological mechanisms involved in bronchiectasis are unknown, with the currently accepted theory being the 'vicious cycle' theory proposed by

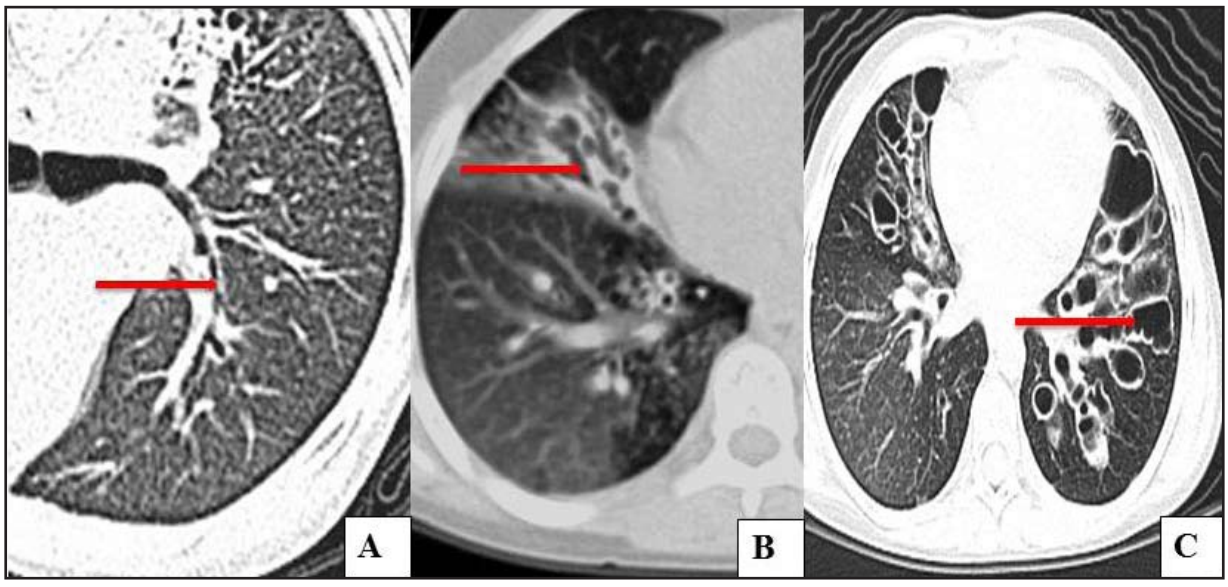

Fig. 1. Stages of bronchiectasis according to the Reid classification system. High-resolution computed tomography views of different stages of bronchiectasis with arrows indicating the abnormalities: A: cylindrical bronchiectasis; B: varicose bronchiectasis; C: saccular bronchiectasis.

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Cole in the mid-eighties (Fig. 2).[8] Cole's theory evolves around an initial 'hit' or trigger that results in airway inflammation. The inflammatory process is established such that, with subsequent lung infections, persistent airway inflammation occurs. This is associated with release of pro-inflammatory cytokines, interleukin (IL)-6, IL-8 and neutrophil elastase.[9-11] These cytokines recruit inflammatory mediators, whose end product is mucous gland hypertrophy and mucus hyperproduction. Excess mucus compromises the mucociliary escalator, which further perpetuates microbial invasion of the airway.

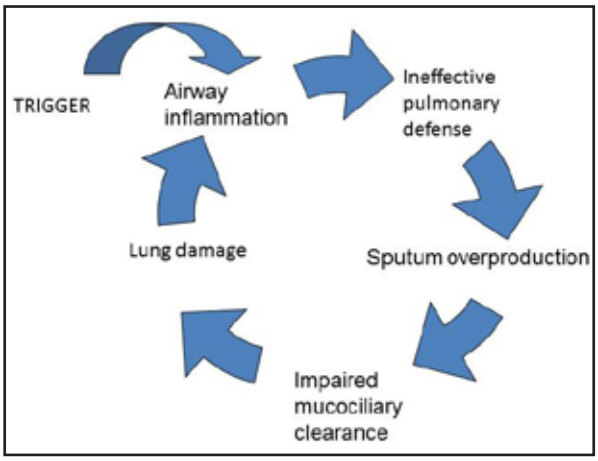

Fig. 2. Proposed pathophysiology of bronchiectasis by Cole.[8]

Innate immune defences

The innate immune system involves both physical barriers, which provide mechanical defences, and cells and mediators involved in the innate immune system.

Physical barriers

Epithelium

The respiratory mucosa is resistant to infection because of the presence of tight junctions between the epithelial cells, which form a physical barrier to infection by pathogens. It also produces antibacterial peptides, which aid in innate immune function. The presence of pathogens induces the airway epithelium to release inflammatory cytokines, which include IL-8, macrophage inflammatory protein 2, tumour necrosis factor alpha (TNF-α)[12] and intracellular adhesion molecule 1 (ICAM-1).[13] ICAM-1 facilitates the migration of macrophages across the epithelium into tissues under the influence of TNF-α and IL-1 (Table II).

Cilia

The respiratory tract is composed mainly of a stratified pseudoglandular ciliated epithelium. The cilia perform a critical function of clearing pathogens and foreign material from the airway by 'sweeping' out the inhaled particles trapped in the mucus blanket. Cilia move in a co-ordinated fashion and move at a rate of 1-2 cm/min.[14] In the upper airways, cilia propel particles towards the pharynx where they are swallowed, while in the lower airways they are propelled towards the trachea, and are subsequently coughed up.[7] Any large variety of defects which affect the ciliary physical ultrastructure, the number of cilia, and the co-ordination of the sweeping movements may result in bronchiectasis.

Mucus

The goblet cells, serous and mucus glands in the submucosa of the airway produce mucus. The mucus blanket found in the airway is about 5-10 µm in depth. Mucus performs an innate immune function property in the lungs by acting as the first barrier in the airways. Mucus is made up of mucin proteins (2-3%), water (95%), surfactant phospholipids, peptides and defence proteins (defensins), and salts.

The superficial part of mucus is moved by the cilia while the deeper periciliary layer is not affected by the cilia. The salt concentration of the mucus layer is critical in the inhibition of bacterial growth. Abnormalities in the salt content are classically present in cystic fibrosis (CF) bronchiectasis, where periciliary fluid dehydration also impacts ciliary movement and function.

Many changes may occur to the mucous properties of patients with chronic inflammatory lung disease.[15] Goblet-cell hyperplasia contributes to excessive mucus production. In the presence of infection, epithelial cells modulate the recruitment of inflammatory cells by the production of chemokines, cytokines, adhesion molecules and modulation of expression of receptors. The presence of persistent infection and impairment of the protective mucociliary escalator, as well as the presence of enzymes such as elastase, cause damage to the airway and lung tissue.[16]

In bronchiectasis the rheological properties of mucus are abnormal with variation in the rheology depending on the cause of bronchiectasis. The cause of bronchiectasis seems to impact the rheological properties of the mucus, which in turn affects the therapeutic intervention that can be used. In childhood post-infective bronchiectasis, mucus is less viscous and more transportable than that of children with CF.[17]

The agents used for airway clearance are either airway hydrators or mucolytics. Mucolytic agents reduce mucus viscosity and promote clearance of secretions. They do this via several mechanisms, which include disruption of disulphide bonds and liquefying proteins that degrade DNA filaments and actin. This modality of treatment is an attractive option in a condition where increased mucus tenacity and viscosity is a problem. Recombinant DNAse (rhDNAse) has been used with excellent results in CF. However, in non-CF bronchiectasis such results are not obtained. In a large multicentre trial by O'Donnell *et al.*, rhDNAse was found to have detrimental effects in participants with worsening decline in lung function.[18] Forced vital capacity (FVC) was reduced by 3.1% compared to that in the placebo group. Patients in the intervention group also suffered an increase in the number of exacerbations. This finding is in contradistinction to the benefits documented in CF. This may have several explanations. Firstly, there are differences in rheological properties of mucus in the CF airway when compared to the non-CF bronchiectactic airway.[17] Secondly, in CF, the pathology is mostly in the upper lobes, and the use of mucolytics may facilitate clearance with gravity, while in non-CF bronchiectasis the lower lobes are affected and this may hamper their effective clearance of thin secretions against gravity.[18,19] Therefore, the use of this drug is strongly discouraged in patients with non-CF bronchiectasis. The use of mucus hydrators, such as hypertonic saline and mannitol has been studied. Hypertonic saline has shown benefit in one small adult study when used in conjunction with chest physiotherapy.[20] A Cochrane review and a recent trial of the use of mannitol showed benefit by changing the physical properties of mucus in fourteen adults with bronchiectasis.[21,22]

Numerous defence proteins and peptides are found in mucus. The defensins and cathelicidins have been found to act against bacterial, viral, yeast and fungal antigens in the airways. These molecules are unusual in that they are amphipathic peptides, i.e. they have both hydrophilic and hydrophobic properties that enable them to disrupt membranes of microbes.[7] The defensins are small (29-

Table II. Inflammatory and anti-inflammatory cytokines and chemokines involved in chronic inflammation*

	Cytokine	Source	Mechanism
Th1	IL-1β	Macrophages	↑neutrophil production bone marrow, ↑TNF-α and IL-6 production, ↑MMP production, ↑COX-2 production and ↑adhesion molecules and chemokines and ↑histamine release
	IL-6	Mononuclear phagocytes, T-cells	↑Liver production of APR, ↑growth factors for mature B cells and increase IL-2 expression
	IL-8	Macrophages, activated T-cells	Chemotactic migration and activation of neutrophils, monocytes, eosinophils and lymphocytes to inflammatory site; ↑neutrophil adherence to endothelium by ICAM-1 upregulation
	TNF-α	Activated macrophages and monocytes	PGE2 synthesis, induction of APR production by liver
	INF-γ	Activated T cells and NK cells	↑MHC class I and II expression on nucleated cells, ↑effector functions of mononuclear phagocytes. Activation of macrophages to kill intracellular pathogens
	G-CSF	Monocytes, fibroblasts and endothelial cells	Stimulates neutrophils, perpetuates eosinophil activation and survival
	GM-CSF	Monocytes, fibroblasts and endothelial cells	Stimulates neutrophils, perpetuates eosinophil activation and survival
Th2	IL-2	Activated T-helper cells	Growth factor/activator for T cells, NK cells and B cells Promotes the development of LAK cells. Increased lymphokine secretion of IFN-γ, IL-3, IL-4, IL-5 and GM CSF
	IL-4	CD4+ T cells, mast cells	Induces CD4+ T cells to differentiate into Th2 cells, promotes Ig class switching to IgG1 and IgE, stimulates collagen and IL-6 production
	IL-5	CD4+ T-helper cells and NK cells	Eosinophil differentiation and activation and stimulation of Ig class switching to IgA, stimulates IgE production and mast cell/eosinophil stimulation
	IL-13	Th2 lymphocytes	Increases CD23 expression and induces IgG4 and IgE class switching
	IL-17	Activated T lymphocytes	Stimulation of IL-6 and IL-8 production and ↑ICAM-1 expression
Chemokines	MIP-1β	Monocytes	Chemotactic migration and activation of monocytes, lymphocytes to inflammatory site
	MCP-1	Monocytes	Chemotactic migration and activation of neutrophils, monocytes, eosinophils, lymphocytes to the inflammatory site
	IP-10	Monocytes, fibroblasts and	Chemoattractant of activated T cells, NK cells, dendritic cells and monocytes
Anti-inflammatory	IL-4	T cells	Inhibits production of pro-inflammatory cytokines: IL-1, IL-6, IL-8 and TNF–α
	IL-6	Phagocytes and T cells	Inhibits TNF-α and IL-1 and increases IL-ra
	IL-10	CD4+ T cells, activated CD8+ T cells and activated B cells	Inhibits IFN–γ production by NK cells, inhibition of IL-4 and IFN-γ induced MHC class II expression on monocytes and reduction of antigen-specific T cell proliferation
	IL-1ra	Immune complexes, neutrophils, macrophages	Inhibits IL-1 by competitive binding to the IL-1 receptor and induces IL-6 synthesis
	IL-13	Th2 lymphocytes	Inhibiting the production of inflammatory cytokines, such as IL-1β, IL-6, IL-8 and TNF–α

↑ - increase; Th - T helper; IL - interleukin; TNF-α - tumour necrosis factor alpha; MMP - metalloproteinase; COX - cyclooxygenase; APR - acute phase reactants; ICAM - intracellular adhesion molecule; PGE2 - prostaglandin E2; INF-γ - interferon gamma; MHC - major histocompatibility complex; G-CSF - granulocyte colony stimulating factor; GM-CSF - granulocyte macrophage colony stimulating factor; NK cells - natural killer cells; ; LAK – lymphokine-activated killer cells; Ig – immunoglobulin; MIP-1β - macrophage inflammatory protein-1 beta; MCP-1 - monocyte chemotactic protein-1; IP-10 - interferon gamma inducible protein-10; IL-1ra - interleukin 1 receptor antagonist.

* Adapted from Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. Front Biosci 1997;2:d12-d26.

47 amino acid) cationic microbicidal peptides that can be divided into 2 families, i.e. the alpha (α)-defensins (produced by the neutrophil azurophilic granules) and beta (β)-defensins (produced by airway epithelial cells). Defensins are known primarily for their antimicrobial activities; however, the scope of their activities extends beyond immune responses and some of these functions could contribute to lung injury.[23]

The cathelicidins are α-helical cationic peptides that are produced by neutrophils. The cathelicidin LL-37 is an antimicrobial peptide produced by neutrophils and respiratory epithelial cells that has similar roles in lung immunity to the defensins.[24] LL-37 is an important host defence peptide that is upregulated in infection and inflammation, specifically in the human lung, and was shown to enhance the pulmonary clearance of the opportunistic pathogen *Pseudomonas aeruginosa in vivo*, by as yet undefined mechanisms.[25] In addition to its direct microbicidal potential, LL-37 can modulate inflammation and immune mechanisms in host defence against infection, including the capacity to modulate cell death pathways.

The surfactant phospholipids involved are the surfactant proteins A and D (Sp-A and Sp-D). These are produced by the type-II alveolar pneumocytes and the previously named 'clara cells'.[26] Sp-A and Sp-D bind to a wide range of pathogens and consequently cause suppression of their growth, damage the microbial membranes and bind and opsonise infectious pathogens.[27] They also affect the local innate immune function by modulating the phagocytosis of macrophages and facilitating the detoxification and removal of lipopolysaccharides in alveolar macrophages.

Innate immune system

Toll-like receptor and non-toll-like receptor pathways

Pathogens interact with the host's immune system via specific pattern recognition proteins, to interact with the innate immune system for rapid clearance of the organism, through downstream activation of chemokines and cytokines. The innate immune system is activated by pathogen associated molecular patterns (PAMPs), which are recognised by pattern recognition receptors such as toll-like receptors (TLRs).[28]

The recognition of pathogens by the immune system begins with TLRs, which are a family of cell surface receptors that can trigger both the innate and adaptive immune systems. Currently eleven TLRs have been recognised and these are expressed in a variety of cells in response to bacterial, viral and fungal infections. The end result of TLR activation is the release of a variety of cytokines, i.e. TNF-α, IL-1β and IL-6, which act on neutrophils and macrophages as their targets. TLR activation triggers a cascade resulting in the activation and nuclear translocation of nuclear factor κβ (NF–κβ) with subsequent release of pro-inflammatory cytokines IL-1β, IL-8 and TNF-α.[29] In addition to this TLR2 and TLR3 also induce mucus production in the airway.[30,31]

The nucleotide oligomerisation domain (NOD)-like receptors form a large group of intracellular receptors that are independent of the TLRs in their activation of the immune system. NOD-like receptors act by increasing the levels of NF-κβ found in the cell nucleus with subsequent activation of receptor-interacting protein kinase (RIPK2) a potent enzyme that induces apoptosis.[32] Twenty-three NOD-like receptors have been identified, and of these NOD-1 and NOD-2 are the most specific for Gram-negative peptidoglycans.

Natural killer cells

The natural killer (NK) cells are large granular lymphocytes that are capable of killing infected cells independent of antigen specificity. They are a type of cytotoxic lymphocyte, critical in the innate immune system, as they rapidly respond to virally infected cells and detect the major histocompatibility complex (MHC) presented on infected cell surfaces, triggering lysis and apoptosis. NK cells are unique, however, as they have the ability to recognise stressed cells in the absence of MHC, allowing for a much faster immune reaction. They were named 'natural killers' because of the initial notion that they do not require activation in order to kill cells that are missing 'self' markers of MHC class 1.

Triggering receptor expressed on myeloid cells

The triggering receptor expressed on myeloid cells (TREM)-1 is a 30 kDa glycoprotein of the immunoglobulin superfamily and is expressed on myeloid cells. It is coded for by genes residing on chromosome 6. TREM-1 has been found to be critical in the innate immune system via its action of amplifying the host's response to microbial agents in the presence of TLR2 or TLR4 ligand-mediated responses. TREM-1 has a short intracellular domain and when bound to ligands, associates with a signal transduction molecule, DAP12, which triggers secretion of inflammatory cytokines (MCP-1, IL-6, IL-8, granulocyte macrophage colony stimulating factor (GM-CFS) and TNF–α), that amplify the host's response to microbial agents and also reduce the production of the anti-inflammatory cytokine IL-10.[33-36] TREM-1 is mainly expressed in blood neutrophils, alveolar macrophages and monocytes. TREM also triggers degranulation of neutrophils, calcium mobilisation and tyrosine phosphorylation of mitogen-activated proteins (ERK1 and ERK2).[35] The membrane-bound form of TREM-1 is liberated by the proteolytic cleavage of its extracellular domain, by MMPs to produce a soluble form (sTREM-1). sTREM is a 27 kDa protein that can be identified in biological fluids and is upregulated on phagocytic cells in the presence of bacteria *(P. aeruginosa, Staphylococcus aureus)* and fungi such as *Aspergillus fumigates*.[37] TREM-1 has also been implicated in neutrophil/platelet interactions, with subsequent mediation of platelet-induced activation of neutrophils.[38] sTREM is demonstrating promise as an inflammatory biomarker of acute infection in various pulmonary conditions.[39-41] A previous study in CF has shown that CF monocytes are 'locked in' with endotoxin tolerance and demonstrate low levels of sTREM.[42]

Neutrophils

In normal individuals macrophages make up more than 90% of cells in airway secretions. Neutrophils mediate their action by engulfing microbes and secreting antimicrobial substances (proteases). Neutrophils are integral to the innate immune mechanisms in the lung, with neutrophilic inflammation being central in the pathogenesis of bronchiectasis.

Elevated levels of neutrophil-derived products IL-6, IL-8 and TNF-α have been found in the sputum of adults with stable bronchiectasis.[43] Transepithelial migration of neutrophils from the intravascular compartment occurs in a co-ordinated fashion, with interplay of various adhesion molecules. Three families of adhesion molecules mediate this: selectins, integrins CD11/CD18 and the immunoglobulin superfamily, i.e. ICAM-1 and vascular adhesion molecule (VCAM)-1.[44] These adhesion molecules are upregulated in the presence of IL-1, IL-8 and TNF-α. Both VCAM-1 and ICAM-1 have been found to be elevated in bronchiectasis subjects.[45] Adherent neutrophils migrate to the inflammatory site under

the direction of the neutrophil chemoattractant IL-8.

Once activated, neutrophils produce neutrophil elastase (NE) and matrix metalloproteinase (MMP)-8 and MMP-9. NE is an omnivorous enzyme produced during phagocytosis and neutrophilic cell death. NE has three main mechanisms of action. Firstly, it has proteolytic effect from its toxic products that digest the airway elastin, basement membrane collagen and proteoglycans.[46] Secondly, it induces the release of cytokines IL-6, IL-8 and GM-CSF.[44] Finally, it is a powerful secretagogue, inducing expression of mucin gene MUC5AC, via the generation of reactive oxygen species.[44] In CF the free elastase is associated with reduced opsonisation of pathogens, thus acting as a potent stimulator for IL-8 production.[47]

Neutrophils also have a third mechanism by which they kill pathogens, with the so-called neutrophil extracellular traps (NETs). NETs are an extracellular fibril matrix whose function is to disarm pathogens as well as to produce antimicrobial proteins such as NE, cathepsin G, myeloperoxidases and histones that kill pathogens independent of phagocytic uptake. NETs also act as a physical barrier that prevents further spread of pathogens. Excessive function of these NETs has been found to contribute to acute lung injury.[48] The NETs are pathogenic against bacteria and fungi in the lung.

Macrophages

Macrophages are derived from the same progenitor cells as dendritic cells. They therefore share common properties of activity against pathogens especially bacteria. Alveolar macrophages are key in the innate immune function of the lung as they phagocytose and kill bacteria in the lungs. Macrophage actions include phagocytosis and endocytosis of pathogens, secretion of cytokines and migration of pathogens to local lymphoid tissue. Macrophages produce a variety of microbicidal molecules that include nitric oxide and reactive oxidation species (ROS) that phagocytose bacteria.

The cytokines produced on macrophage stimulation include TNF-α, IL-1β, interferon (INF)-α, INF–β, IL-6, IL-12 and IL-18 which are pro-inflammatory cytokines, as well as IL-10 and tumour growth factor beta (TGF–β), both anti-inflammatory cytokines. Macrophages also inhibit the inflammatory damage in the airway by phagocytosing apoptotic neutrophils and cellular debris, via the production of the anti-inflammatory cytokines.

Adaptive immunity

Specific humoral immunity

There are key adaptive immune responses, which are mediated by pathogen-specific immunoglobulins (Igs). In bronchiectasis the role of secretory IgA, a key mucosal surface Ig, is unclear, although a higher level of IgA2 has been found in the pulmonary tissue when compared to blood (30% compared to 10-20%). IgA2 has also been found to be more resistant to IgA-specific proteases produced by bacteria.[49]

IgG-mediated opsonisation of bacterial facilitates phagocytosis of pathogens. IgG is critical in the maintenance of the integrity of the airway and a marked deficiency of IgG results in bronchiectasis. In CF-related bronchiectasis, IgG levels are associated with a poorer prognosis, which is postulated to be related to higher antigenic exposure from systemic presentation of antigens through damaged airway mucosa.[50-52] IgG2 may impair phagocytosis and high levels of IgG2 antibodies are found in CF and human immunodeficiency virus (HIV)-associated disease.[53,54]

Specific cellular immunity

The primary effector cells of T-cell immunity are the T lymphocytes, which are characterised by the CD8+ cytotoxic T cells. The CD8+ T cells medicate their function by allowing for recognition of epitopes of infected cells by the NK cells and by direct antimicrobial activity against pathogens. The CD4+ T cells (T-helper cells) also secrete cytokines, which enhance the adaptive immune function of those of CD8+ T cells.

The classic example of T-cell depletion is in HIV infection where a depletion of these cells results in recurrent bacterial, fungal and viral infection and subsequent bronchiectasis.

Cytokines and chemokines

Cytokines are intracellular signalling molecules whose function is to regulate the proliferation, differentiation and activation of immune cells.[55] Cytokines have many physiological functions, which assist in the organism's response to micro-organisms, as well as being key in inflammatory and anti-inflammatory responses. The major pro-inflammatory cytokines in bronchiectasis are TNF-α, IL-6, IL-8, IL-12 and INF-α. These cytokines play a role in inflammation by mediation of vasodilatation, increased vascular permeability and upregulation of cellular adhesion molecules. All the direct activities of these cytokines are beyond the scope of this review.

GM-CSF is a potent chemokine that allows prolonged survival of neutrophils in the airway. The intensity of the pro-inflammatory cytokines was also found to be elevated in subjects with colonisation of the airway by micro-organisms. This elevation in cytokines, coupled with the elevated proteases released from neutrophils, namely NE, MMP-2, MMP-6 and MMP-9, overwhelm the antiprotease defence mechanisms, rendering the lung vulnerable to destruction.[47,56,57] MMP-9 levels have been found to correlate with IL-8 and lung function in children with CF.[58] The use of antibiotics has been shown to result in a reduction of these pro-inflammatory cytokines.[59-62]

CONCLUSION

The immune system entails complex machinery, which involves both physical and chemical barriers whose aim is to protect the airway from antigenic damage. Although a large amount of duplication does occur, all the component parts seem necessary to maintain the integrity of the airway. Any deficiency or excessive action of any part thereof may result in lung tissue destruction, excessive inflammation and subsequent bronchiectasis. Increasing knowledge of the various components may aid in not only diagnosis of disease, but may also impact future targeted therapeutic interventions for the management of bronchiectasis.

Declaration of conflict of interest

The author declares no conflict of interest.

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