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Immune regulation in idiopathic bronchiectasis

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Bronchiectasis is a complex pathological endpoint arrived at through a diverse interplay between lung infection and altered immune function. It comprises irreversible, abnormal dilatation of one or more bronchi, with chronic airway inflammation and is associated with recurrent chest infections, airflow obstruction, chronic cough, excessive sputum production, and malaise. Many pathogens are associated with this disease, including chronic bacterial infections, nontuberculous mycobacteria, and aspergillis. However, the etiology is poorly defined. Disease-associated genes indicate a likely contribution to disease mechanism both from innate and adaptive immunity. The role of immune mechanisms is highlighted by the occurrence of bronchiectasis in a subset of patients with rheumatoid arthritis or inflammatory bowel disease as well as diseases of immune dysregulation such as combined variable immune deficiency, transporter associated with antigen processing (TAP) deficiency syndrome, and hyper-IgE syndrome. Recent evidence indicates a possible role of excessive natural killer cell activation in pathogenesis.

Keywords: bronchiectasis; chronic lung infection; allergic bronchopulmonary aspergillosis; NK cells; aspergillus; immunity

Bronchiectasis is commonly defined as an irreversible, abnormal dilatation of one or more bronchi, with chronic airway inflammation.[1] This is associated with recurrent chest infections, airflow obstruction, chronic cough, excessive sputum production, and malaise. However, the underlying etiology is poorly defined, and these may best be regarded as common clinical and pathological endpoints, potentially resulting from diverse underlying causes. Evidence suggests that during the latter part of the 20th century, when the incidence of bronchiectasis might have been expected to fall due to changes in immunization and antibiotic prescribing, the disease became more common—an increase probably not attributable simply to improved detection.[2] It had been thought that the prevalence of bronchiectasis was decreasing in the developed world as a result of childhood immunizations, increased use of antibiotics, and decreased tuberculosis. A U.S. retrospective study for the period 1993–2006 showed an average age-adjusted annual increase in hospitalizations of 2.4% in men and 3.0% in women.[2] The explanation for this apparent paradox may lie in the assumption that bronchiectasis should be regarded as neither a simple susceptibility to chronic infection nor as a physical defect of the bronchi, but as a complex endpoint of the interplay between microbial pathogens, host microbiota, and the influence of these on host regulation of inflammation and adaptive immunity.

Different populations show considerable differences in prevalence of the disease, an observation most likely related to differences both in genetics and environment, as discussed later. In Australian Aborigines[3] and Alaskan native children, the prevalence is 14 per 1,000, compared with around 1 per 1,000,000 in Finnish children.[4]

The majority of bronchiectasis cases are described as idiopathic insofar as no causal, initiating factor is identifiable. Other causes include postinfectious, immune deficiency–associated, and allergic bronchopulmonary aspergillosis (ABPA).[1] There is also

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an interesting subset of patients in which bronchiectasis is associated with autoimmune disease, most notably, rheumatoid arthritis and ulcerative colitis. This list of associated, predisposing factors exemplifies the mechanistic conundrum of this disease process: since the work of Peter Cole in the 1980s, it has been argued that this should be considered the result of a vicious cycle of chronic infection and dysregulated, excessive inflammation.[5] Certainly, a key feature, both of bronchiectasis and ABPA, is the chronic interleukin (IL)-8–mediated homing of neutrophils to the lung.[6,7] It is also possible that neutrophil migration is promoted by IL-17 release from lung T cells, gamma delta ($\gamma\delta$)) cells, and natural killer (NK) cells responding to local bacterial infection. However, this is a disease endpoint that may be arrived at either by deficiencies in immunity (notably immunoglobulin deficiencies and transporter associated with antigen processing (TAP) deficiency syndrome, in which there is abrogated TAP function necessary for the proper expression of HLA class I molecules loaded with antigenic peptide)[8] or by conditions that might be regarded as comprising excessive, dysregulated immune effector mechanisms, such as rheumatoid arthritis and ulcerative colitis. Although bronchiectasis is evidently not primarily autoimmune in etiology, there are important clues to an underlying mechanism offered by the appearance of these symptoms in a proportion of patients with these autoimmune conditions.[9,10] Furthermore, combined variable immune deficiency (CVID) patients are prone to both bronchiectasis and to a wide range of autoimmune pathologies.[11]

It is interesting to consider the role of *Aspergillus fumigatus* as a trigger for bronchiectasis in the context of this spectrum of immune competence. Infection with aspergillus may elicit diverse host Th1/Th2/Th17 subset polarization depending on several factors, including immunogenetic background and metabolic status of the fungal spores themselves.[12,13] In the context of immune hyperreactivity, lung exposure to fungal spores may lead to immunopathologically mediated ABPA. However, impaired immunity will predispose to invasive aspergillosis with pathology dependent on fungal enzymes. In general, patients with chronic lung disease show enhanced susceptibility to *A. fumigatus* colonization and infection.[14]

Hyper-IgE syndrome, or Job's syndrome, an immune deficiency resulting from mutations in the STAT3 cytokine signaling transducer, is associated with raised IgE, highly impaired Th17 immunity, and an elevated proinflammatory profile with respect to tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ).[16,17] Furthermore, it has been proposed that defective generation of IL-10–induced tolerogenic dendritic cells and inducible regulatory T cells may contribute to proinflammatory changes.[18] This immune defect underlines the fact that bronchiectasis can be regarded not simply as an outcome from insufficient immunity but from dysregulated control of the innate and adaptive response to infection. Around two-thirds of these patients manifest bronchiectasis among a range of clinical symptoms that also includes dermatitis, mucocutaneous infections due to *Staphylococcus aureus* and *Candida,* as well as pneumonia, mostly caused by *S. aureus* or *Streptococcus pneumoniae.*[15] Around one half of hyper-IgE patients with structural lung disease have invasive fungal disease.[19]

Bronchiectasis is generally associated with increased susceptibility to a number of specific pathogens including *Haemophilus influenza*, *H. parainfluenzae*, *Pseudomonas aeruginosa*, *S. pneumoniae*, *Moraxella catarrhalis*, *S. aureus*, *Stenotrophomonas maltophilia*, Gram-negative enterobacter, nontuberculosis mycobacteria (NTM), and aspergillus. The prevalence of NTM in patients with bronchiectasis is 2%, with mycobacterium avium complex (MAC) the most frequent NTM isolated. *P. aeruginosa* and *S. aureus* are frequently cocultured. Bronchiectasis patients with NTM show a higher prevalence of coexisting aspergillus-related lung disease.[20]

Genome-wide association studies have not been undertaken for idiopathic bronchiectasis, but a number of candidate gene polymorphisms associated with innate and adaptive immunity have been investigated. Although no association has been found with functional polymorphisms for TLR4 or TLR2,[21] an IFN-γ polymorphism and a CXCR-1 polymorphism, which influences IL-8 binding and neutrophil trafficking, were strongly associated with bronchiectasis risk following colectomy in ulcerative colitis, though not with enhanced bronchiectasis risk per se.[22] HLA class II analysis shows an association with HLA-DRB1$*$0101 and HLA-DQB1$*$0501, both commonly present in linkage disequilibrium in the same DR1 haplotype.[23] This might be

interpreted to indicate a classical immune response gene effect with respect to adaptive immunity to a key microbial pathogen involved in triggering disease. In line with this notion, $CD4^+$ T cells are indeed found in lung biopsy tissue from patients, although $CD8^+$ T cells are if anything more abundant.[24] This presumably indicates an additional, common component to microbial pathogenesis that has not yet been substantially investigated, whether viral in nature or dependent on intracellular bacteria.

Potential roles for other cell types in immunopathogenesis are indicated by more indirect evidence. The rare individuals with TAP deficiency syndrome suffer from a much more specific spectrum of infections and pathologies than might perhaps be predicted for a defect as fundamental to adaptive immunity as the inability to load antigenic peptides into the peptide-binding groove of HLA class I molecules for presentation to T cells. Within this spectrum of pathologies is bronchiectasis.[8] It has been suggested that this and other defects in mucosal immunity in these families may be a consequence of abnormal activation of NK cells or $\gamma\delta$ T cells, downstream of the HLA class I loading defect.

Alterations in NK cell activation are currently a source of intense analysis in a very wide range of conditions, spanning tumors, infections, autoimmunity, and inflammation. NK cells were once considered simply "null" cells—lymphocytes lacking the specific antigen receptors of either B cells or T cells and yet capable of spontaneously lysing tumors or herpesvirus-infected targets.[25,26] This view was followed by a period in which a model was developed to account for experiments showing that NK cell activation ensued from recognition of cells through downregulated expression of HLA class I molecules.[27] In the past 20 years, it has become clear that NK cells follow a very complex program of counterpoised receptor families that impart an integrated array of activating and inhibitory signals to the nucleus.[28]

Furthermore, NK cells are likely to be as diverse as $CD4^+$ T cells in terms of cellular subsets, expressing different receptors and differentiation markers and follow different transcriptional programs, from proinflammatory to anti-inflammatory, in addition to effects that feed into subsequent polarization of adaptive T cells immunity. The NK cell paradigm has also shifted to encompass the fact that, far from being limited to recognition of tumors and herpesviruses, they haves roles in immunity to autoantigens as well as to bacterial, viral, fungal, and parasite antigens.

NK cells are considered to be extremely important in the normal functioning of lung host defense.[29,30] Current models of NK cell activation have focused in part on the component of activation dependent on the interaction between HLA class I molecules and a large family of cognate receptors—the killer immunoglobulin-like receptors (KIR). The KIR genes are encoded on human chromosome 19q13.4 as a string of genes of variable number and identity between individuals. Depending on the signaling domains attached to their cytoplasmic tails, an immunoreceptor tyrosine-based inhibition motif (ITIM) or an immunoreceptor tyrosine-based activation motif (ITAM), KIRs may impart an inhibitory or activating signal, respectively. This is an extreme form of immune diversity within and between populations: there is considerable variation of geography and ethnicity in the composition of KIR haplotypes.[23] The significance of the interesting observation that some populations, such as aboriginal Australians who have the highest prevalence of bronchiectasis, also tend to carry some of the most activating KIR haplotypes has yet to be elucidated. There is further diversity and complexity due to the fact that different individuals within a given population will carry different numbers of activating and inhibitory KIR genes and different polymorphic variants of these genes.[31] Furthermore, the impact of the KIR repertoires will vary depending on whether a given individual also carries the cognate HLA class I polymorphic variant with which the KIRs interact. Finally, there is variegated expression of KIR gene products, such that they are differentially expressed on the NK cells (and T cells) within an individual. In analysis of our UK idiopathic bronchiectasis cohort, HLA-C group 1 homozygosity, specifically, the HLA-Cw*03 allele, was associated with disease.[23,32] Around 50% of this cohort was HLA-C group 1 homozygous, compared with 25% of controls. It would be predicted that fewer NK cells would fall under inhibitory control if the ligands for inhibitory receptors are absent. In bronchiectasis, there is a preponderance of only HLA-C group 1 with the activating KIRs 2DS1 and/or 2DS2. Such combinations might be predicted to contribute to a highly

activated (and potentially proinflammatory) NK cell program.[32]

Concluding remarks

Bronchiectasis is a pathological endpoint resulting from a complex interplay between lung infection and immunity. The interaction both with diverse forms of immune deficiency of distinct immune pathways and with a subset of autoimmune patients offers particular conceptual challenges. Recent immunogenetic analysis, predicting a pathogenic role for excessive NK cell activation, may offer new therapeutic options.

Conflicts of interest

The authors declare no conflicts of interest.

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