Exploring immune dysfunction in bronchiectasis: a focus on natural killer cells using single-cell transcriptomes

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To the Editor:

Bronchiectasis is characterised by persistent airway inflammation, impaired mucociliary clearance and recurrent respiratory infection [1]. Despite its increasing prevalence and clinical burden, the systemic immune mechanisms contributing to disease progression remain poorly understood [1, 2]. Recent advances in single-cell RNA sequencing (scRNA-seq) have revolutionised our understanding of cellular heterogeneity and immune dysregulation in chronic respiratory diseases, including bronchiectasis [3–5]. A previous study revealed that bronchiectasis pathophysiology predominantly involves bronchial remodelling, with decreased basal cell and increased ciliated cell proportions associated with the Wnt/β-catenin signalling pathway, in which downstream β-catenin signalling regulates airway epithelial differentiation by promoting cell self-renewal and progenitor maintenance [3]. However, the role of immune cells, including monocytes and natural killer (NK)-cells, in modulating lung inflammation has been underexplored. In addition, monocyte-derived macrophages are proinflammatory cells commonly observed in various inflammatory lung diseases. Therefore, we performed scRNA-seq on peripheral blood mononuclear cells (PBMCs) from eight patients with bronchiectasis and eight healthy controls to identify immune alterations associated with bronchiectasis. Single-cell libraries were prepared using 10x Chromium 5′ v2 chemistry. A total of 80 000 cells from 16 individuals were loaded across four GEMs (20 000 cells per GEM; 5000 cells per individual). Cell counts were determined using an automatic cell counter (LUNA-FL, Logos Biosystems). The hash-tag oligonucleotide technique was used for demultiplexing, and the samples were sex- and age-matched. Singlets were identified using scDblFinder and cells with a mitochondrial gene percentage <5% were retained. For quality control, we selected cells with 700–4000 detected features. Batch correction was performed using Harmony. A total of 36 383 high-quality PBMCs were analysed, revealing four major immune compartments: T-cells, B-cells (expressing CD79A, MS4A1 and BANK1), NK-cells and myeloid cells. Cell type annotation was performed based on canonical marker genes from the National Institutes of Health Human Biomolecular Atlas Project reference database.

Baseline demographic and clinical characteristics of the bronchiectasis and control participants are summarised in figure 1a. Global clustering showed no patient-specific clusters, indicating broadly comparable overarching immune architecture between the two groups. The overall peripheral immune landscape and major PBMC clusters are shown in figure 1b. Among T-cell populations, patients demonstrated a noticeable contraction of naïve T-cells (expressing CD3D, CCR7 and selectin L). In contrast, both $CD4^+$ and $CD8^+$ effector memory T-cell (both expressing CD4, interleukin-7 receptor (IL7R), CD3D, CD69, MAL/IL7R, CD8A, CD3D, CCL6 and granzyme B) subsets appeared expanded, giving the overall T-cell compartment a more differentiated and antigen-experienced profile. This pattern was reinforced through Bayesian compositional modelling, which identified high inclusion probabilities for the increase in $CD4^+$ effector memory cells and the reduction in $CD8^+$ naïve T-cells. γδT-cells (expressing TRDC, TRDV2 and CD7) were also consistently diminished across bronchiectasis samples (figure 1c).

Innate immune alterations were even more prominent. Within the NK-cell compartment, a distinct reduction was observed in the $FCER1G^+$ NK subset, which represents a substantial functional fraction of circulating NK-cells (figure 1c and d). This subset normally expresses a suite of chemokines and activating molecules (CCL3, CCL4, XCL1 and XCL2), and its reduction was accompanied by transcriptional evidence of functional stress. Specifically, genes associated with cellular stress responses (*e.g. GADD45B*,

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a)

	Patient (n=8)	Control (n=8)		Patient (n=8)	Control (n=8)
Age, years	63.19 (64–75)	48.25 (28–55)	**Laboratory findings**		NA
Sex, male	6 (75)	6 (75)	WBC count per L	6.8 (5.0–8.4)	
BMI, kg·m^{-2}	23.9 (20.5–27.9)	NA	Neutrophil count per µL	62.6 (43.7–84.5)	
Smoking history		NA	hsCRP, mg·dL^{-1}	0.2 (0.1–0.4)	
Never-smoker	5 (62.5)		Sputum MPO concentration, ng·mL^{-1}	17.0 (11.0–23.6)	
Current or ex-smoker	3 (37.5)				
mMRC scale	1 (0–2)	NA	**Comorbidities**		NA
BHQ score	61.8 (44.7–79.4)	NA	Hypertension	0(0)	
Physiotherapy	1 (12–5)	NA	COPD	0(0)	
Post-bronchodilator spirometry		NA	Asthma	0(0)	
FVC, L	2.8 (1.8–4.0)		Diabetes mellitus	0(0)	
FVC, % predicted	78.0 (58–107)		Cardiovascular disease	1(12.5)	
FEV_1, L	1.8 (1.0–3.1)		Neurological disease	0(0)	
FEV_1, % predicted	71.0 (43–107)		Malignancy	0(0)	
FEV_1/FVC ratio	63.8 (54–76)		Previous history of tuberculosis	0(0)	
Microbiology		NA	Previous history of pertussis	0(0)	
Pseudomonas aeruginosa	7 (57.1)		NTM-PD	0(0)	
Others	2 (28.9)				

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FIGURE 1 a) Baseline characteristics of the bronchiectasis (BE) patients and control group. Data are presented as the median (interquartile range) or n (%). b) Overview of the single-cell RNA sequencing workflow of peripheral blood samples from eight BE patients and eight healthy controls. The hash-tag oligonucleotide technique was applied for sample multiplexing.10x 5′ v2 chemistry was used (created in https://BioRender.com/illustrations/67e243e28985306869c1288b). c) Boxplots illustrating the proportions of each T-cell and natural killer (NK)-cell subset in BE patients and healthy controls. The Mann–Whitney–Wilcoxon test was used for statistical analysis. Left: scCODA shows the Bayesian inclusion probability for the proportion of each cell subset. Right: in the inclusion probability bar graph, cell types marked in white indicate those increased in control group, whereas cell types marked in red indicate those increased in patient group. d) Uniform manifold approximation and projection (UMAP) shows NK-cell clusters in the healthy controls and BE patients (top left), and the box plot shows the proportions of Ec fragment of IgE (FCER1G)$^+$ NK-cells in BE patients and healthy controls (top right). Dot plot showing the expression of marker genes across NK-cell subpopulations (bottom). e) Box plots highlighting downregulated genes related to cellular stress in FCER1G$^+$ NK-cells. f) Dot plot showing the expression of marker genes across monocyte subpopulations. g) Circular plot illustrating ligand–receptor interactions between FCER1G$^+$ NK-cells and other NK-cells and myeloid cells. Lines indicate the presence of ligand–receptor interactions. Circular plots specifically show CCL3–CCR1 and CCL5–CCR1 interactions between FCER1G$^+$ NK-cells and pro-inflammatory CD14$^+$ monocytes. h) Violin plot illustrating the expression levels of CXCR4 in pro-inflammatory CD14$^+$ monocytes in BE patients and healthy controls. The p-value was calculated using a Wilcoxon rank-sum-test. i) An overview of the roles of NK cells and monocytes involved in the systemic pathogenesis of bronchiectasis in this study. (Created in BioRender.com) Cellranger (v7.0.1) was used for sequence alignment. The p-value was calculated using a Mann–Whitney–Wilcoxon test. BMI: body mass index; mMRC: modified Medical Research Council; BHQ: Bronchiectasis Health Questionnaire; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; WBC: white blood cell; hsCRP: high-sensitivity C-reactive protein; MPO: myeloperoxidase; NTM-PD: nontuberculous mycobacterial pulmonary disease; NA: not available; PBMC: peripheral blood mononuclear cell; CTL: cytotoxic T-lymphocyte; Tem: effector memory T-cell; Treg: regulatory T-cell; cCD: conventional dendritic cell; pDC: plasmacytoid dendritic cell; NS: nonsignificant. *: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001.

BRD2 and *IER5*) were downregulated in bronchiectasis-derived FCER1G$^+$ NK-cells (figure 1e), suggesting altered activation states or reduced resilience under inflammatory conditions.

Monocytes displayed additional signs of disruption. While the major monocyte subsets were present in both groups, the transcriptional profile of CD14$^+$ monocytes differed substantially in bronchiectasis. The most notable change was a consistent decrease in CXCR4 expression (figure 1h). Since CXCR4 is a key regulator of monocyte retention and migration, its reduction indicates a shift in monocyte trafficking capacity.

To understand whether these alterations affected intercellular communication, ligand–receptor analyses were performed using CellChat. This revealed a coordinated interaction in signalling between FCER1G$^+$ NK-cells and pro-inflammatory CD14$^+$ monocytes. Pathways involving chemokine pairs such as CCL3–CCR1 and CCL5–CCR1 were detected (figure 1g), pointing to weakened communication within the pro-inflammatory CD14$^+$ monocyte population. Broader monocyte marker expression patterns are shown in figure 1f.

Taken together, these results point toward a multilayered pattern of immune disturbance in bronchiectasis. The disease is characterised by reduced FCER1G$^+$ NK-cells, weakened NK-derived chemokine signalling, altered monocyte trafficking marked by decreased CXCR4 expression and an adaptive immune compartment skewed toward memory phenotypes. A conceptual summary of this interconnected immune imbalance is illustrated in figure 1i.

This study provides evidence of systemic immune dysregulation in bronchiectasis, spanning both innate and adaptive compartments. Chronic airway infection and inflammation are well-established drivers of disease progression [1, 2, 5], and the immune abnormalities identified here offer mechanistic insights into how systemic components may contribute to persistent inflammation. Blood-derived immune signatures have previously been shown to parallel airway immune states in chronic respiratory diseases [3–5], supporting the relevance of PBMC profiling. The depletion of FCER1G$^+$ NK-cells represent a major innate defect. This subset produces chemokines such as CCL3 and CCL4, which activate and recruit monocytes [6, 7]. Reduced FCER1G$^+$ NK-cells may therefore impair early innate immune responses and attenuate monocyte priming. The downregulation of stress-response genes (*GADD45B*, *BRD2* and *IER5*) resembles patterns described in NK-cell exhaustion in chronic inflammatory lung disorders [3–5]. Monocyte dysfunction further supports this impaired innate axis. CXCR4 is essential for monocyte retention, migration and maturation; therefore, reduced CXCR4 expression suggests defective monocyte trafficking and macrophage precursor differentiation [8, 9]. Inefficient monocyte recruitment may contribute to inadequate bacterial clearance and the chronic inflammation typical of bronchiectasis [10–15].

Adaptive immune abnormalities – including reductions in naïve T-cells, increases in effector memory T-cell subsets and reductions in γδT-cells – are consistent with persistent antigenic stimulation. These patterns have been observed in chronic microbial exposure and repeated inflammatory cycles [3, 10–12, 15].

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Reduced γδT-cells may compromise early mucosal defence and epithelial repair, increasing susceptibility to recurrent infections.

Integrating these findings, bronchiectasis appears to involve a disrupted innate–adaptive immune interface characterised by impaired NK–monocyte signalling, reduced monocyte maturation capacity and sustained T-cell activation. These mechanisms may contribute to the chronic inflammation, impaired pathogen clearance and structural airway damage that define the disease.

This study has limitations. All bronchiectasis samples were obtained during a clinically stable phase, with no evidence of active airway infection at the time of sampling. In addition, this study includes modest sample size and reliance on PBMCs rather than airway-derived immune cells. However, the consistency of scRNA-seq findings across individuals and the alignment with known immune biology suggest meaningful systemic signatures. Future studies integrating airway samples, larger cohorts and longitudinal tracking will be essential to evaluate whether these immune alterations may serve as biomarkers or therapeutic targets. Bronchiectasis Severity Index scores were not collected in this cohort, limiting the ability to perform formal severity stratification.

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Author contributions: H. Lee and H.J. Kim are the guarantors of the manuscript and take responsibility for the content of the manuscript, including the data and analysis. B. Yang, D. Kim, H. Lee and H.J. Kim contributed to the conception and design of the study. B. Yang, D. Kim, H. Lee and H.J. Kim were involved in the collection and interpretation of the data. D. Kim, G. Min, I. Jeon and E-G. Kim were involved in statistical analyses. All authors read and approved the final manuscript.

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