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LETTER

Airway epithelial cell cilia transcriptomic dysregulation is associated with the inflammatory phenotype in asthma

To the Editor,

Asthma is a heterogeneous disease in terms of phenotypes and endotypes, characterized by airway remodelling with epithelial dysfunction, including alterations of the mucociliary clearance.¹ Previous studies identified motile cilia dysfunction in severe asthma.^{2,3} Considering the importance of both motile and primary cilia in structural and functional epithelium integrity,^{4,5} we investigated the associations between cilia dysregulation and asthma phenotypes and endotypes using a transcriptomic signature approach.

We explored the transcriptomic signature of the 879 cilia-associated genes in the bronchial airway epithelial cells of 141 patients at a stable state from the U-BIOPRED study (61 severe asthma (SA), 36 mild/moderate asthma (MMA) and 44 healthy subjects). All participants in the UBIOPRED cohort gave written and signed informed consent.⁶ The clustering of patients according to the differentially expressed genes (DEGs; false discovery rate correction applied) identified two groups, one of which with high cilia dysregulation (Appendix S1) being enriched in asthmatics (51.4% SA, 34.3% MMA vs 40.6% SA, 22.6% MMA, $p=.04$), and characterized by high total IgE ($p=.022$), high eosinophil counts in blood ($p=.001$) and in sputum ($p=.03$), and low FEV₁ ($p=.02$) (cilia dysregulated group) (Table S1, Figure S1).

To further analyse the associations between cilia dysregulation and SA, we next focused on the SA population of both groups, comparing the 18 SA with high cilia dysregulation (SAd) with the other 43 SA. The SAd group was characterized by older age at diagnosis ($p=.016$), lower BMI ($p=.010$), less frequent GERD ($p=.023$), a more severe airway obstruction ($p=.017$) and a trend towards more frequent male gender ($p=.059$, Table 1). Exacerbation history and treatment did not differ between the groups. The SAd group was further characterized by high blood eosinophil ($p=.023$) and basophil counts ($p=.011$, Figure 1A); high sputum eosinophil count ($p=.013$, Table 1), less frequent paucigranulocytic sputum phenotype (0/7 vs 9/18, $p=.024$); higher concentrations of the T2-related cytokines IL13, CCL17 and MIP1b in the plasma (respectively 1.3 ± 1.2 pg/mL vs 0.8 ± 0.6 pg/mL, $p=.038$; 147 ± 108 pg/mL vs 76 ± 62 pg/mL, $p=.001$; 67 ± 20 pg/mL vs 54 ± 20 pg/mL, $p=.011$; Figure 1B), and more abundant macrophages in the bronchial submucosa

(6.14 ± 6.05 cellsmm⁻² vs 3.40 ± 4.54 cellsmm⁻², $p=.040$) and in the epithelium (1.43 ± 2.42 cellsmm⁻¹ vs 0.12 ± 0.53 cellsmm⁻¹, $p=.0026$; Figure 1C). Epithelial remodelling features including mucus immunostaining did not significantly differ between groups. Thus, the alteration of the cilia-associated genes distinguished severe asthmatics featuring adult-onset, fixed airflow obstruction and T2-high eosinophilic asthma.

We next investigated the global transcriptomic signature of the SAd compared with the other SA, to identify cellular mechanisms associated with cilia dysregulation. The SAd group exhibited 4117 DEGs including 315 cilia-associated DEGs compared with the SA group (Figure 1D). The top 100 DEGs, including three cilia-associated genes (Prokineticin 2, PROK2; Pleckstrin Homology Like Domain Family B Member 2, PHLDB2; and neuropilin-1, NRP1), were almost exclusively upregulated in SAd (Figure 1D,E). The analysis of the biological processes using Reactome database identified the immune system pathway (strength=0.64, FDR=1.61 $\times 10^{-14}$) (Figure S2). Protein-protein interaction network analysis identified cytokine-cytokine receptor interaction (strength=0.93, FDR=8.05 $\times 10^{-6}$) and NF- κ B signalling pathway (strength=1.14, FDR=1.8 $\times 10^{-4}$) as principal KEGG pathways (Figure S3).

Our original experimental approach, although hypothesis generating, and of cross-sectional design with uncertainty regarding the long-term stability of the endotype/phenotype we describe, provided clues of an intriguing, yet unreported link between cilia regulation and inflammation in asthma. Uncontrolled inflammatory mediators may initiate and extend airway remodelling.⁷ We hypothesized that an initial dysregulation of cilia could initiate and extend inflammation in a double whammy. Investigating the origin of altered cilia structure and function in light of the inflammatory response will pave the way towards novel therapeutic strategies in asthma.

In conclusion, we identified a novel endotype of severe asthma centred on dysregulation of the cilia-associated gene signature and unveiled a panel of genes that may orchestrate or maintain epithelial remodelling in asthma via inflammatory modulation. Although our findings rely on a robust European cohort, additional experimental approaches are needed to elucidate the implications for asthma phenotyping.

TABLE 1 Subjects characteristics in the severe asthma (SA) and severe asthma with cilia dysregulation (SAd) clusters.

Clusters	SA	SAd	P Value
<i>n</i>	43	18	
Demography and clinical characteristics			
Age (yrs)	48.1 ± 14.1	52.8 ± 11.7	.112
Age at diagnosis (yrs)	13 [2–35]	38 [10–45]	.016
Sex—F/M	23/20	5/13	.059
BMI (kg/m ²)	32.2 ± 5.9	28.3 ± 5.6	.010
Comorbidities			
Gastroesophageal reflux disease	22 (51.2)	4 (22.2)	.023
Allergic rhinitis	19 (44.2)	10 (55.5)	.344
Nasal polyps	11 (25.6)	7 (38.8)	.257
Never smokers	26 (60.5)	14 (77.8)	.158
Pack-years	5.5 [1.8–21.3]	18.5 [3.3–57.0]	.215
Atopy	33 (76.7)	12 (66.7)	.368
Total IgE (IU/mL)	110 [39–324]	221 [24–715]	.069
Peripheral eosinophil count (10 ⁹ /L)	0.25 ± 0.20	0.39 ± 0.34	.023
0.15–0.29	17 (39.5)	1 (5.5)	.006
≥0.30	13 (30.2)	11 (61.1)	.025
Exacerbations in last 12 months	2 [2–3]	3 [1–4]	.280
Functional and biological characteristics			
FEV ₁ (% predicted)	76.0 ± 21.6	68.4 ± 19.2	.100
FEV ₁ /FVC	67.6 ± 11.7	60.5 ± 12.2	.017
Exhaled NO (ppb)	42.5 ± 29.0	35.7 ± 29.2	.212
Sputum cell count, <i>n</i>	18	7	
Eosinophils (% of total cells)	0.8 [0.310.7]	23.9 [1.4–42.0]	.013
Neutrophils (% of total cells)	46.1 [31.5–65.4]	52.7 [43.7–91.0]	.150
Treatment			
Maintenance oral corticosteroids	18 (41.9)	9 (50.0)	.321
Total daily dose ^a	10.0 [7.5–20.0]	10.0 [5.5–20.0]	
Long-acting β agonist	42 (97.7)	18 (100)	.705
Tiotropium bromide	7 (16.3)	4 (22.2)	.450
Leukotriene receptor antagonist	27 (62.8)	6 (33.3)	.031

Note: Values are means ± standard deviation, medians [interquartile ranges] or absolute numbers (percentages). Percentages given are derived from those subjects with valid data.

^aNormalized to Prednisolone.

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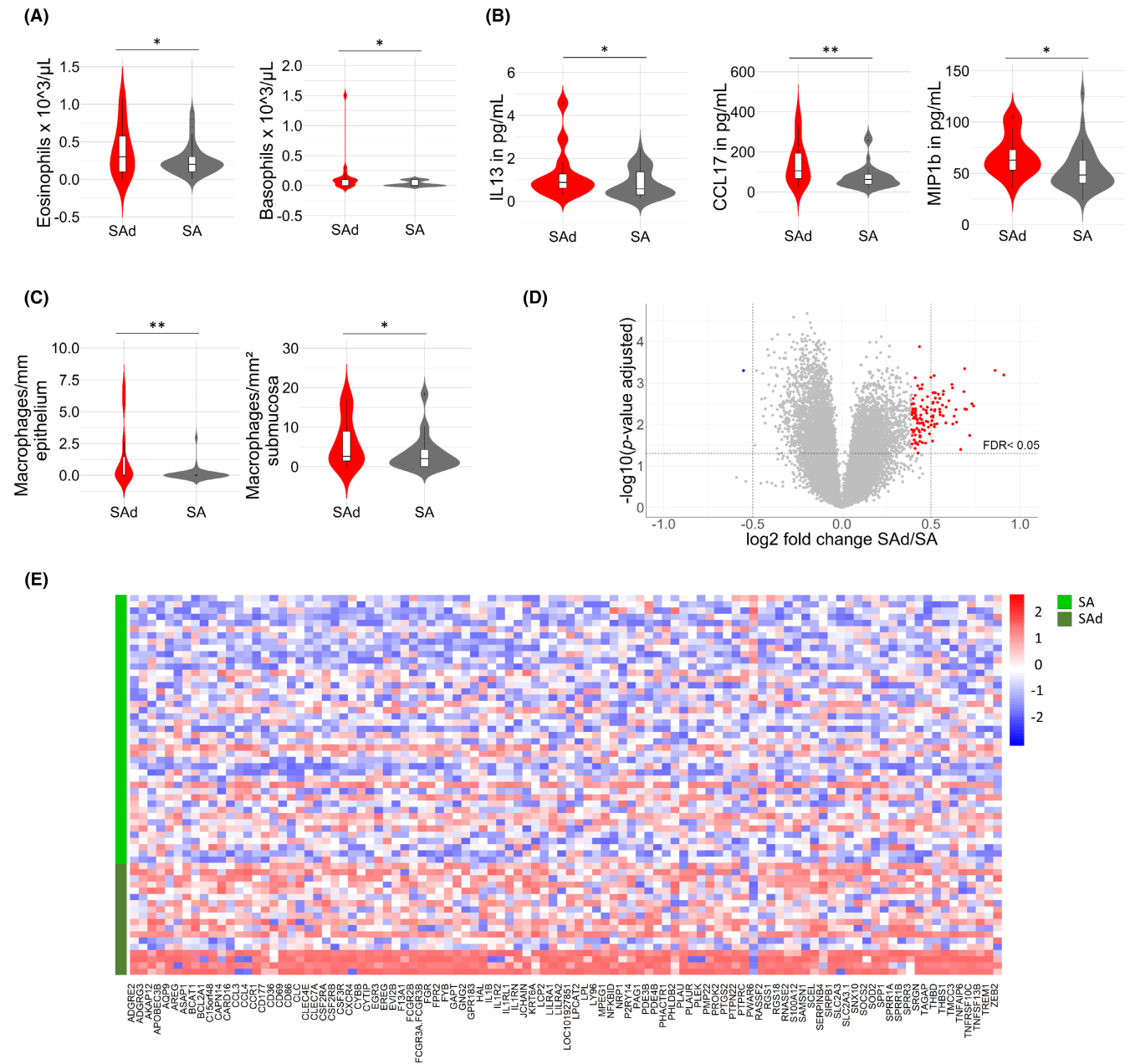


FIGURE 1 The alteration of the cilia-associated transcriptomic signature in SA defines an endotype with exacerbated immune dysregulation. Violin plots showing (A) eosinophil and basophil concentrations in the blood, (B) IL-13, CCL17 and MIP1b concentrations in the plasma, and (C) epithelial and submucosal macrophage counts in the biopsies of the 18 SAAd vs the remaining 43 SA. (D) Volcano plot of statistical significance against fold-change in \log_2 scale between SAAd and SA highlighting the significantly top 100 DEGs in SAAd transcriptomes. (E) Heatmap of the 100 most DEGs identified in the SAAd transcriptomes. The patients are organized in order of mean absolute deviation in transcript levels of the 400 cilia-associated transcripts. * $p < .05$, ** $p < .01$.

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AUTHOR CONTRIBUTIONS

Study concept: V. Dormoy and J.M. Perotin; study design: JM Perotin; acquisition data: M.A. Devilliers, A. Brisebarre, S.J. Wilson and J.M. Perotin; analysis and data interpretation: M.A. Devilliers, A. Brisebarre, L.M.G. Petit, G. Deslée, R. Djukanović, V. Dormoy and J.M. Perotin; revision of manuscript: M.A. Devilliers, M. Polette, G. Deslée, R. Djukanović, V. Dormoy and J.M. Perotin; manuscript writing: M.A. Devilliers, V. Dormoy and J.M. Perotin.

CONFLICT OF INTEREST STATEMENT

G. Deslée reports lecture honoraria from Chiesi, AstraZeneca and GlaxoSmithKline; outside the submitted work. R. Djukanović reports receiving fees for lectures at symposia organized by Novartis, AstraZeneca and TEVA, consultation for TEVA and Novartis as member of advisory boards, and participation in a scientific discussion about asthma organized by GlaxoSmithKline. He is a co-founder and current consultant and has shares in Synairgen, a University of Southampton spin out company. V. Dormoy reports lecture honoraria from Chiesi and AstraZeneca; outside the submitted work. J.M. Perotin reports lecture honoraria from AstraZeneca and support for attending meetings from AstraZeneca and Chiesi; outside the submitted work. There are no further conflicting interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Heijink IH, Kuchibhotla VNS, Roffel MP, et al. Epithelial cell dysfunction, a major driver of asthma development. *Allergy*. 2020;75:1902-1917.
2. Thomas B, Rutman A, Hirst RA, et al. Ciliary dysfunction and ultrastructural abnormalities are features of severe asthma. *J Allergy Clin Immunol*. 2010;126:722-729.e2.
3. Perotin J-M, Wheway G, Tariq K, et al. Vulnerability to acid reflux of the airway epithelium in severe asthma. *Eur Respir J*. 2022;60:2101634.
4. Belgacemi R, Diabasana Z, Hoarau A, et al. Primary ciliogenesis is a crucial step for multiciliated cell determinism in the respiratory epithelium. *J Cell Mol Med*. 2021;25(15):7575-7579.
5. Perotin J-M, Polette M, Deslée G, Dormoy V. CiliOPD: a ciliopathy-associated COPD endotype. *Respir Res*. 2021;22:74.
6. Shaw DE, Sousa AR, Fowler SJ, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J*. 2015;46(5):1308-1321.
7. Jesenak M, Durdik P, Oppova D, et al. Dysfunctional mucociliary clearance in asthma and airway remodeling – new insights into an old topic. *Respir Med*. 2023;218:107372.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.