

Raised blood eosinophil counts are associated with high airway type 2 inflammation in chronic obstructive pulmonary disease

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Raised BEC is associated with airway type 2 inflammation, supporting the potential benefit of anti-IL-5 therapy in COPD with an eosinophilic phenotype

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Background

- COPD is a complex respiratory disease with high unmet treatment needs¹
- Type 2 inflammation, as characterised by raised eosinophils, drives COPD pathophysiology and increases the risk of exacerbations, which in turn drive health deterioration, worsening symptoms and QoL and increased morbidity and mortality²
- ECLIPSE was a longitudinal, observational study that explored identification of genetic factors or biomarkers that correlate with COPD subtypes and may help predict disease progression³

Aims

To investigate the association between type 2 inflammation gene signatures and clinical and phenotypic biomarkers via microarray-based transcriptomics on patient sputum and blood from ECLIPSE

Methods

ECLIPSE (GSK ID: 104960; NCT00292552) exploratory analysis: Study design

ECLIPSE: A longitudinal, observational study of patients with COPD

Patient eligibility criteria

- Post-bronchodilator FEV₁ <80% predicted
- Post-bronchodilator FEV₁/FVC ≤0.7
- Patients classified by GOLD criteria

Molecular analysis

Type 2 inflammation gene set (24 genes)

Assessed using microarray-based transcriptomics

GSVA score* calculated per patient

Analyses

Analysis 1

- Examine the relationship between sputum transcriptomics-based GSVA for canonical type 2 geneset across patients stratified by BECs and GOLD stage

Analysis 2

- Examine the relationship between plasma IL-5 relative protein expression and blood eosinophils

*GSVA score is a measure of the activity level of a biological pathway or gene set within a sample

Results

Table 1: Clinical metadata parameters, thresholds and sample sizes used to define subgroups for type 2 GSVA score comparisons in transcriptomic analysis

	Sputum transcriptomics (N=144)	Plasma protein (N=1544)
Disease severity*		
GOLD 2 (moderate)	59 (41)	N/A
GOLD 3 (severe)	72 (50)	N/A
GOLD 4 (very severe)	13 (9)	N/A
Blood eosinophils†		
<100 cells/μL	20 (14)	N/A
≥100–<300 cells/μL	64 (45)	N/A
<150 cells/μL	38 (26)	603 (39)
≥150 cells/μL	74 (51)	941 (61)
<300 cells/μL	84 (58)	1206 (78)
≥300 cells/μL	28 (19)	338 (22)
Missing	32 (22)	N/A

Data are presented as n (%). *GOLD 2 (moderate): FEV₁ ≥50–<80% predicted; GOLD 3 (severe): FEV₁ ≥30–<50% predicted; GOLD 4 (very severe): FEV₁ <30% predicted; †Blood eosinophil thresholds reflect counts of 0.15 and 0.30 GI/L (150 and 300 cells/μL); 32 samples had missing values for paired sputum samples and were excluded from this analysis

Figure 1: In paired samples, GSVA score indicating type 2 inflammatory signature was associated with sputum eosinophils, raised blood eosinophil levels and GOLD stage

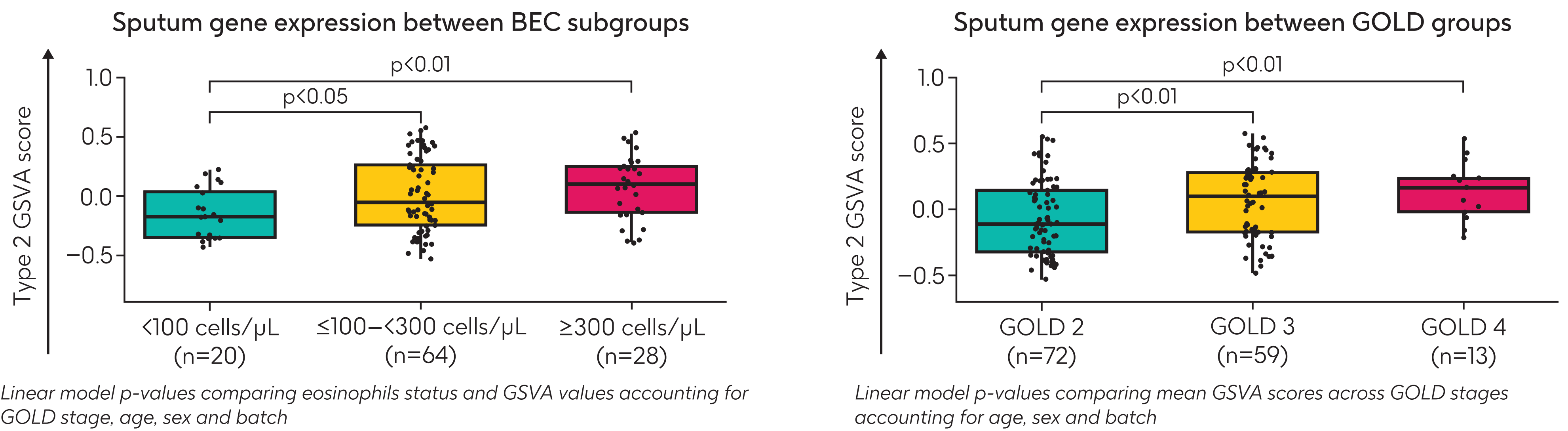
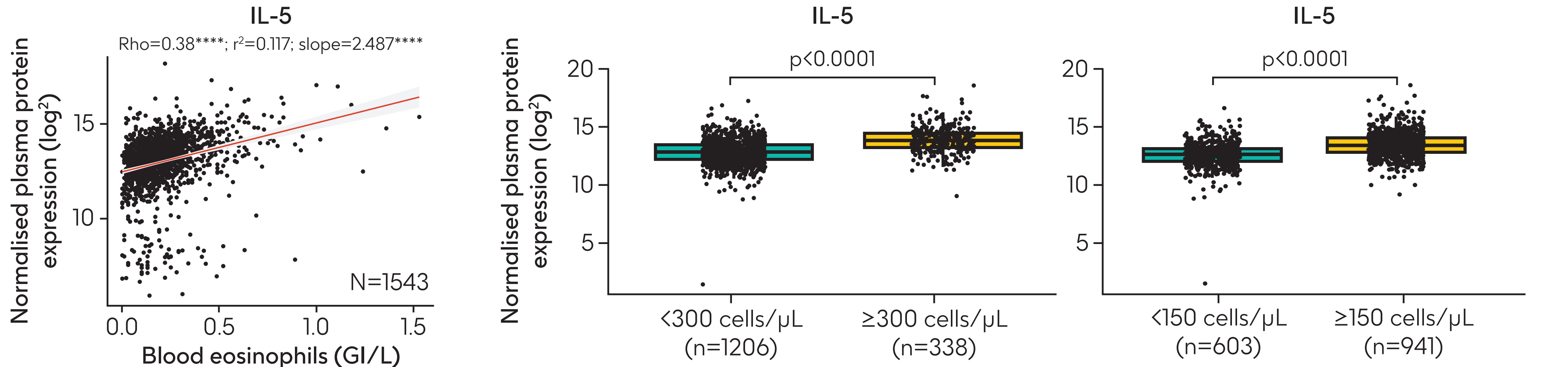


Figure 2: BEC is correlated with plasma type 2 IL-5 levels, which are elevated in those with high BEC versus low BEC



Asterisks represent either Spearman's correlation (rho) or linear model (r² or slope) p-values comparing mean normalised plasma protein versus blood eosinophil sequencing batch for ECLIPSE cohort patients with COPD. ****p<0.0001 *FDR adjusted p-values comparing blood eosinophil status and normalised protein expression values using the proteome-wide Limma differential analysis framework

Conclusions

Raised BEC is associated with increased type 2 inflammation gene expression in COPD sputum and plasma, providing a mechanistic explanation for the benefits observed with anti-IL-5 therapy in clinical trials^{4,5}

Type 2 GSVA score in sputum was positively associated with blood eosinophil levels

The findings also show that eosinophilia (blood or sputum) is a widely shared pathological feature in COPD independent of disease severity

Abbreviations

BEC, blood eosinophil count; COPD, chronic obstructive pulmonary disease; FDR, false discovery rate; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GI/L, giga per litre; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GSVA, gene set variation analysis; IL-5, interleukin-5; N/A, not applicable; QoL, quality of life

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Disclosures

JW, SC, JB, JM, SK and RC are employed by GSK and hold financial equities in GSK.