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Sputum IL-5 Concentration Is Associated with a Sputum Eosinophilia and Attenuated by Corticosteroid Therapy in COPD

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Abstract

Background—Airway inflammation in chronic obstructive pulmonary disease (COPD) is predominately neutrophilic, but some subjects demonstrate eosinophilic airway inflammation. Whether these inflammatory phenotypes have differential cytokine and chemokine expression is unknown.

Objectives—To assess the sputum concentrations of cytokines and chemokines and their response to oral corticosteroid therapy in COPD subjects with or without a sputum eosinophilia.

Methods—Cytokine and chemokine concentrations were measured using the meso-scale device platform. To assess validity, recovery of exogenous spikes was examined. The concentrations of the validated mediators were measured in COPD sputum from subjects with or without a sputum eosinophilia. In a subgroup with a sputum eosinophilia, the response to oral prednisolone 10 mg for 1 month was examined.

Results—The recovery in sputum of exogenous spiked mediators was >80% in 11/26 cytokines and chemokines. In supernatants from eosinophilic (n = 39) versus non-eosinophilic (n = 59) sputa, the geometric mean (95% CI) concentration was increased for IL-5 [9.0 (4.5-18) pg/ml vs. 3.6 (2.7-6.3) pg/ml, p = 0.03]. IL-5 alone was correlated with sputum eosinophil counts (r = 0.33, p = 0.001), and was attenuated following treatment with prednisolone [n = 9; mean difference 2.3 pg/ml (0.2-4.3), p = 0.032].

Conclusion—We have validated the use of the meso-scale device platform for cytokine and chemokine measurements in the sputum supernatants in COPD. Sputum IL-5 was associated with a sputum eosinophilia and was attenuated following oral corticosteroid therapy. Whether this cytokine is important in the pathogenesis of COPD in a subgroup of patients warrants further investigation.

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Conflicts of Interest

M.M., P.R., P.D. and P.N. are employed by AstraZeneca R&D Charnwood. I.D.P. received USD 2,000 for speaking at conferences organised by GlaxoSmithKline and USD 5,000 for speaking at conferences organised by AstraZeneca, and has received a grant of USD 500,000 from GlaxoSmithKline for a study in severe asthma. C.E.B. has received a total of USD 2.2 million in research funds from AstraZeneca, Cambridge Antibody Technology and GlaxoSmithKline, he has received less than USD 10,000 in consultancy fees from Cambridge Antibody Technology, AstraZeneca, GlaxoSmithKline, Roche and Pfizer, and has participated in scientific meetings organised and financed by AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, MSD and Pfizer.

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Keywords

Airway inflammation; Chronic obstructive pulmonary disease; Cytokines; Eosinophil; Interleukin-5

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [1, 2]. It is characterised by progressive airflow limitation, with pulmonary and systemic inflammation, partly mediated by locally secreted cytokines and chemokines [3]. The identification of key inflammatory mediators may yield further novel therapies to improve symptoms and reduce exacerbations.

Airway neutrophilia and CD8+ T lymphocyte infiltration have been the hallmarks of COPD inflammation [4] with increased numbers of CD8+ T lymphocytes associated with worsening severity of disease [5]. However, sputum and airway wall studies in COPD have also shown the presence of eosinophilic inflammation [6-8]. This evidence supports that eosinophilic inflammation (≥3% sputum eosinophil count) is present in up to 40% of COPD patients in stable disease [9], and randomised control trials have shown that this type of inflammation is associated with a favourable response to corticosteroid therapy [10] with reduction in severe exacerbation rates [11].

Whether the cytokine and chemokine concentrations are differentially expressed in the sputum supernatants from COPD subjects with or without eosinophilic inflammation is unknown. Several studies have examined the concentration of mediators in sputum supernatants, but to date the measurement of only a few of these mediators has been validated. The development of high throughput platforms such as the meso-scale device has presented the opportunity to measure a large panel of mediators in small volumes of sputum supernatants. Therefore, in this study our aim was to assess the validity, repeatability and responsiveness of measuring cytokines and chemokines using a meso-scale device in sputum supernatants from COPD subjects.

Methods

Subjects

Ninety-seven sputum supernatant samples were available from 34 COPD subjects with stable disease, who had participated in a 12-month longitudinal randomised control study looking at eosinophilic airway inflammation and exacerbation rates [11]. This included baseline samples from 13 subjects. The clinical characteristics of the 34 subjects included in this study are shown in table 1. Subjects were recruited from the respiratory clinics at Glenfield Hospital (Leicester, UK) between February 2003 and March 2004. All subjects had a medical diagnosis of COPD, as per the GOLD criteria [2]. The study was approved by the Leicestershire, Rutland and Northamptonshire ethics committee, and all subjects gave signed written consent.

Measurements

We recorded baseline characteristics that included age, gender, smoking history and exacerbation frequency in the previous year. At each visit we recorded spirometry (Vitalograph, Maids Moreton, UK), before and after bronchodilation following 400 μg inhaled salbutamol, and health status using the chronic respiratory health questionnaire [12]. Sputum was collected from subjects, and processed, as previously described, to produce

cytospins for differential cell counts and supernatant for fluid-phase measurements using dithiothreitol (DTT) [13]. Cytokine and chemokine levels were measured using the meso-scale device platform.

Subgroups

The sputum supernatant chemokine and cytokine concentrations were measured to address the following aims: (1) to define the pattern of chemokine and cytokine concentrations in supernatants from samples with or without sputum eosinophilia (≥3% non-squamous cells) at stable state, including baseline; (2) to assess the repeatability of cytokines and chemokines identified in (1) as differentially expressed between eosinophilic and non-eosinophilic patients and the relationship between these mediators and the intensity of eosinophilic inflammation, and (3) to investigate the response of the mediators identified in (2) from COPD subjects with a sputum eosinophilia following treatment with prednisolone 10 mg daily for 1 month.

Meso-Scale Measurements

Meso-scale multi-array platforms were used to measure multiple chemokines and cytokines. The meso-scale platform (Meso Scale Discovery, Gaithersburg, Md., USA) uses electroluminescence technology, where antibodies have been lined in a patterned array to measure multiple mediators simultaneously. We assessed 26 mediators in duplicate. This required a minimum of 150 μl of sputum DTT cell-free supernatant for all analysis. The use of mucolytic dithiothreitol (DTT) in the processing of the sputum samples using the meso-scale multi-array platform was validated using sputum samples from COPD subjects with stable disease. The limit of detection of cytokine and chemokine recovery from the meso-scale platform is presented in table 2.

To assess recovery, standard chemokine or cytokine spike was added to the sputum samples and to buffer controls (n = 5), and then validated for its concentration by comparing spike recovery from sputum and buffer controls. A recovery of >65% from sputum identified initial analytes with a satisfactory recovery. Further analysis was then performed on these analytes that demonstrated a percentage recovery from sputum compared to buffer of at least 80% [14].

Analysis

Statistical analysis was performed using Prism version 4. Parametric data were expressed as mean (SEM), data that had a log normal distribution were log transformed and described as geometric mean (95% confidence interval) and non-parametric data were described as median (range). One-way analysis of variance and Student's t tests were used for across and between group comparisons, respectively, for parametric data, and Wilcoxon matched paired test was used for non-parametric data. Correlations were assessed by Pearson and Spearman correlations for parametric and non-parametric data and repeatability assessed by intra-class correlation coefficients. A p value of <0.05 was taken as the threshold for statistical significance.

Results

Recovery of all cytokines and chemokines measured by the meso-scale multi-array platform are illustrated in figure 1. Recovery was >80% in 11/26 mediators and the chemokines CXCL8 and CCL22 were found to be the most abundant.

Baseline sputum samples were available in 13 COPD subjects, of which 6 had a sputum eosinophilia. We found differential expression in the eosinophilic versus non-eosinophilic

group at baseline for IL-5 only with a mean (SEM) of 4.46 (1.62) versus 0.47 (0.12) pg/ml, p = 0.02, respectively (see fig. 2).

For all sputum supernatant samples (n = 97), the pattern of expression of the 11 validated cytokines and chemokines was different between the COPD samples with and without evidence of eosinophilic inflammation (table 3). Compared to the samples with non-eosinophilic inflammation those with eosinophilic inflammation had increased concentrations of IL-5 (mean difference 0.4 pg/ml, 95% CI 0.2-0.9, p = 0.03). There was no difference in the dosage of inhaled corticosteroid in the eosinophilic group versus the non-eosinophilic group (mean (SEM) 1,200 (130) vs. 1,346 (152), p = 0.94).

The repeatability of IL-5 was assessed in paired sputum samples from 9 stable COPD subjects separated by 4 weeks, whilst the subject was stable without evidence of an exacerbation 6 weeks before the baseline sample and without changes in the subjects' treatment between visits. For IL-5 the Pearson correlation coefficient (r) was 0.78 and the intra-class correlation was 0.34.

IL-5 was the only cytokine which significantly correlated with the sputum eosinophil count (r = 0.33, p = 0.001; fig. 3). There was no correlation of IL-5 with FEV_1 percent predicted or health status as measured by the CRQ_{total} (r = 0.03, p = 0.73 and r = 0.07, p = 0.51, respectively).

Paired samples from another 9 COPD subjects with eosinophilic inflammation were available before and after treatment with prednisolone 10 mg/day for 1 month. Following corticosteroid therapy there was a significant reduction in IL-5 (mean difference 2.3 pg/ml, 95% CI 0.2-4.3, p = 0.032) and sputum eosinophil count (mean difference 6.0%, 95% CI 3.2-8.7, p = 0.001; figure 4), whilst there was a non-significant increase in lung function and health status following corticosteroid therapy (table 4).

Discussion

We have validated the measurement of 11 cytokines and chemokines in sputum supernatants from subjects with COPD using the meso-scale device platform. We report here for the first time that in COPD sputum, IL-5 concentration was increased in those sputum samples with evidence of eosinophilic inflammation compared to those without. The sputum IL-5 concentration was repeatable, related to the degree of sputum eosinophilia and decreased in response to systemic corticosteroids. Therefore, sputum IL-5 is a valid, repeatable and responsive measure in COPD.

The meso-scale multi-array platform employs a sandwich immunoassay format, where antibodies are lined in a patterned array. We have been able to demonstrate the use of this format in the analysis of sputum supernatant from COPD subjects demonstrating good recovery of several cytokines and chemokines. Detection of many cytokines, including that of sputum IL-5 using enzyme-linked immunosorbent assay (ELISA), has previously proven difficult in asthmatics [15], improved only upon the addition of protease inhibitors [16]. The use of DTT is known to reduce detectable levels of mediators measured by ELISA or substrate assay [17]; however, using the meso-scale platform and DTT for our samples, we were able to get recovery of >80% for 11/26 analytes including IL-5, without the need for protease inhibitors.

In this study we found differential expression of IL-5 in subjects with and without sputum eosinophilia, demonstrating an increase in IL-5 concentrations in those with sputum eosinophils. IL-5 is a T helper 2 cytokine, and is integral to the development, differentiation, recruitment, activation and survival of eosinophils [18]. The evidence for IL-5 is established

in asthma, with new therapies aimed at blocking IL-5 production [20]. Despite the overlap between asthma and COPD, current dogma suggests that IL-5 does not play a role in stable COPD, irrespective of disease severity [19, 21]. In bronchial biopsies IL-5 is consistently not elevated in COPD [22, 23]. In contrast, Betz et al. [24] found that sputum IL-5 was increased in asymptomatic subjects with airway hyper-responsiveness and subjects with COPD compared to healthy controls, although correlation with sputum eosinophils was not examined [24]. Our study extends this earlier observation to show that the sputum IL-5 concentration was increased in COPD sputum samples with eosinophilic inflammation.

In addition to an increased sputum IL-5 concentration, in those COPD samples with an eosinophilia, we identified a positive, albeit weak, correlation between the sputum IL-5 and eosinophil count. This correlation has previously been observed only in asthmatic subjects. Interestingly, in response to systemic corticosteroid therapy there was a reduction in the sputum eosinophil count and sputum IL-5 concentration. This is similar to studies conducted in asthmatic patients [25], further demonstrating similarities to COPD and identifying the role of IL-5 in COPD subjects with an eosinophilic phenotype. This relationship infers that blocking IL-5 may be a novel therapeutic strategy in COPD [20]. In addition to increase of IL-5 in our non-eosinophilic group, we have noted that there was a trend towards reduction of TNF-α and CD120b in the non-eosinophilic group. Pulmonary and systemic inflammation in COPD has shown elevated pro-inflammatory mediators, but whether this inflammation is differential according to the corresponding airway inflammation warrants further analysis.

One potential limitation of our study is that we only looked at sputum samples obtained, whilst patients were stable and not during exacerbations. Sputum eosinophilia is known to be increased in exacerbations of COPD [26], and more so in those with a viral aetiology [27]. Further studies measuring IL-5 and infective parameters during an exacerbation are required. The numbers of subjects studied before and after corticosteroid therapy were small and not placebo controlled, but the magnitude of the response of the sputum eosinophil count and IL-5 suggests this observation is robust. Other studies of cytokine and chemokine concentration in sputum have been limited to small panels of mediators and have confronted several technical difficulties.

We were able to validate the meso-scale discovery platform using DTT processed samples and without the need for protease inhibitors. This multi-array high throughput device removes the length of the assay time, the small dilutional range known to occur with ELISA, whilst requiring small quantities of analyte.

In conclusion, we have demonstrated differential expression of the cytokine and chemokine pattern in COPD sputum samples with and without an eosinophilia using the meso-scale discovery platform. Importantly, sputum IL-5 was increased in samples with an eosinophilia, which was correlated with the intensity of eosinophilic inflammation and responsive to systemic corticosteroid therapy. Whether in a subgroup of COPD subjects IL-5 is an important cytokine in the pathogenesis of disease, a potential biomarker to guide steroid responsiveness or a novel therapeutic target warrants further investigation.

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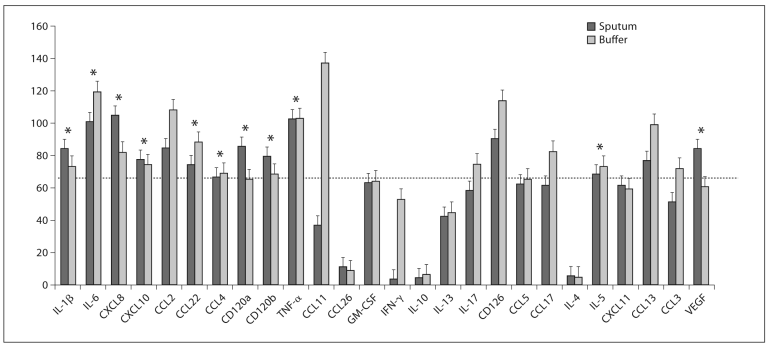

Fig. 1.

Percentage recovery of exogenous spike of cytokine and chemokines to COPD sputum and buffer samples (n = 5). Horizontal bar set at 65% recovery to highlight analytes with sufficient recovery from sputum. Asterisked analytes considered to be valid assays, with recovery of >80% from sputum compared to buffer. Data presented as mean (SEM).

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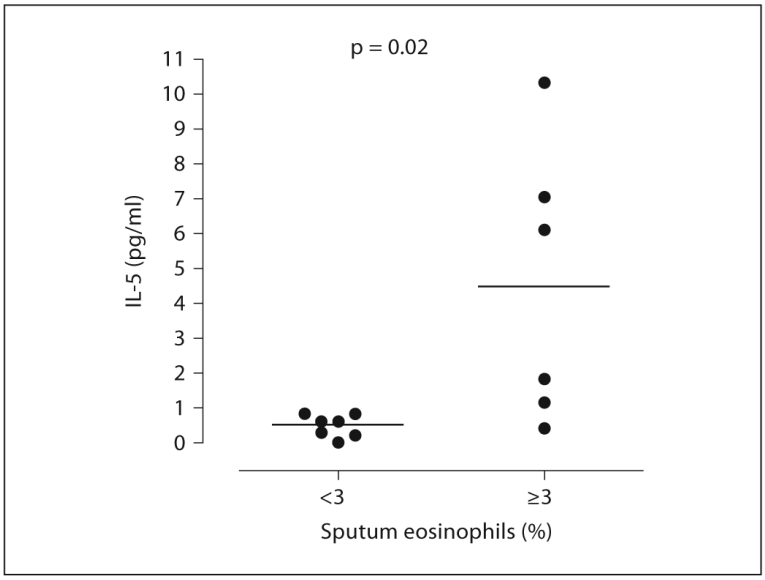

Fig. 2.
Mean IL-5 concentrations in subjects according to sputum eosinophil (<3 or ≥3%) counts at baseline visit.

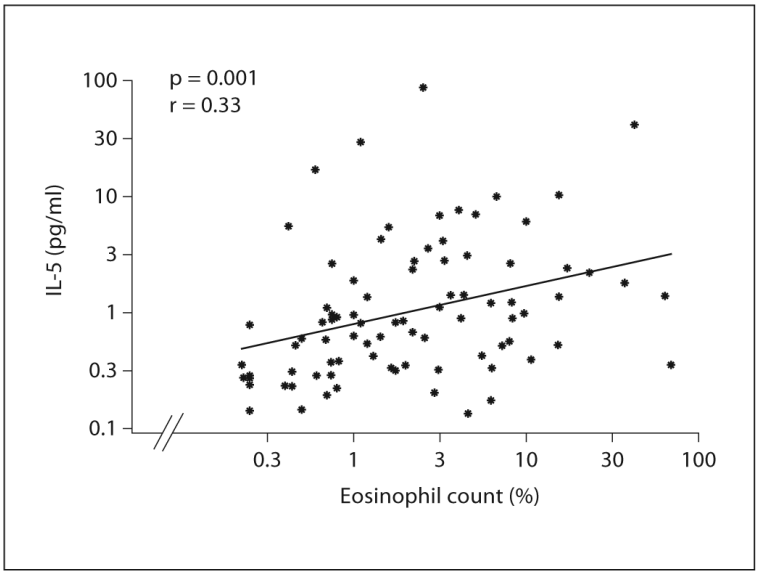

Fig. 3.
Correlation between sputum IL-5 concentration and sputum eosinophil differential cell count.

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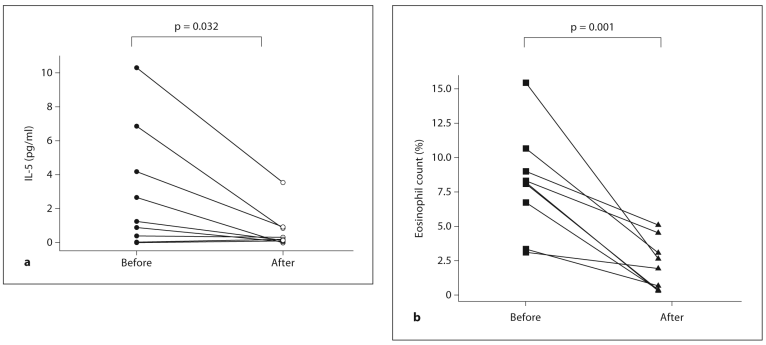

Fig. 4.

IL-5 concentration (pg/ml; **a**) and sputum eosinophil count (%; **b**) before and after oral prednisolone for 1 month (n = 9).

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Table 1

Baseline clinical characteristics of COPD subjects

	COPD subjects (n = 34)
Age, years	68 (52-80)
Female/male, n	6/28
Current smoker, %	27
Ex-smoker, %	74
Smoking pack-years	45 (4.5)
Baseline inhaled steroid dose/day[a]	1,290 (174)
Exacerbations in previous year	2.8 (0.4)
FEV_1, l	1.0 (0.1)
FEV_1 % predicted	36.0 (2.3)
FEV_1 post-bronchodilator, l	1.1 (0.1)
FEV_1/FVC, %	47.6 (2.0)
CRQ_{TOTAL}	15.4 (0.7)

Data presented as numbers (range), simple percentages or as mean (SEM), as appropriate.

[a]Beclomethasone dipropionate equivalent.

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Table 2

Limit of detection of cytokines and chemokines from meso-scale discovery platform (pg/ml)

Cytokine	LD (mean)	Chemokine	LD (mean)
IL-1β	0.7	CCL2	5.9
IL-4	0.3	CCL4	9.8
IL-5	0.1	CCL3	119.0
IL-6	2.6	CCL5	0.3
IL-10	1.6	CCL11	4.9
IL-13	18.4	CCL13	20.0
IL-17	4.5	CCL17	8.0
IFN-γ	1.0	CCL22	256.7
TNF-α	1.4	CCL26	3.0
CD120a	10.0	CXCL8	0.2
CD120b	0.8	CXCL10	32.9
CD126	0.2	CXCL11	6.2
GM-CSF	2.3	VEGF	9.7

LD = Lower detection limit.

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Table 3

Cytokine and chemokine concentrations (pg/ml) of sputum supernatant samples categorised by sputum eosinophil count

	Eosinophil <3% (n = 58)	Eosinophil ≥3% (n = 39)	p value
IL-1β	509 (298-871)	248 (158-392)	0.06
IL-6	4,125 (2867-5,938)	3,335 (2,419-4,600)	0.41
CXCL8	31,830 (19,626-51,623)	30,602 (22,415-41,768)	0.90
CXCL10	8,471 (6,324-11,346)	7,038 (5,700-8,692)	0.35
CCL22	13,510 (11,615-15,712)	11,291 (9,418-13,540)	0.13
CCL4	4,718 (3,207-6,940)	7,332 (4,924-10,405)	0.11
CD120a	6,228 (4,576-8,476)	4,314 (3,440-5,411)	0.08
CD120b	2,158 (1,457-3,198)	1,255 (899-1,752)	0.05
TNF-α	123 (82-186)	69 (47-103)	0.05
IL-5	4 (3-6)	9 (5-18)	0.03
VGEF	8,319 (6,542-10,579)	7,595 (6,293-9,167)	0.58

Data presented as geometric mean with 95% CI in parentheses.

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Table 4

Sputum cytokine and chemokine concentrations, lung function and health status before and after 1 month of prednisolone 10 mg (n = 9 COPD subjects)

	Before corticosteroid therapy	After corticosteroid therapy	Mean difference (95% CI)	p value
Eosinophils, %	8.1 (1.2)	2.2 (0.6)	6.0 (3.2 to 8.7)	0.001
FEV_1, l	0.95 (0.1)	0.97 (0.1)	-0.01 (-0.17 to 0.13)	0.78
FEV_1 % predicted	37.7 (6.5)	39.0 (7.4)	-1.3 (-7.0 to 4.5)	0.62
CRQ_{total}	15.8 (1.3)	16.2 (1.4)	-0.4 (-2.5 to 1.6)	0.64
IL-5, pg/ml	3.0 (1.2)	0.7 (0.4)	2.3 (0.2 to 4.3)	0.032

Data presented as mean (SEM), unless otherwise indicated.