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LETTER OPEN ACCESS

Oncostatin-M Is Produced by Human Eosinophils and Expression Is Increased in Uncontrolled Severe Asthma

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Keywords: allergy | asthma | bronchoalveolar lavage | CRSwNP | cytolysis | degranulation | eosinophils | Oncostatin M | severe asthma

To the Editor,

The development of airway remodeling in asthma is believed to be a consequence of airway inflammation, including eosinophilia, a hallmark of asthma and asthma severity. We previously found that eosinophil products activate fibroblasts, with IL-1, oncostatin-M (OSM) and TNFSF12 as predicted eosinophilic factors responsible for fibroblast activation [1]. OSM, a member of the gp130 ligand family of cytokines, is produced by immune cells, but it is typically not recognized as an eosinophilic product. OSM has been associated with asthma severity and lower lung function [2], and it was reported that OSM upregulates gene expression levels that may promote airway granulocytic inflammation and mucus production [2]. In nasal polyps (NP) of patients with chronic rhinosinusitis (CRS),

Abbreviations: ACQ, asthma control questionnaire; APC, antigen-presenting cells; BAL, bronchoalveolar lavage; BALF, BAL fluid; BE, bronchial epithelial; CRSwNP, chronic rhinosinusitis with nasal polyps; FDR, false discovery rate; IQR, interquartile range; Lap-TGF-b1, latency-associated peptide of TGF-b1; OSM, oncostatin M; OSMR, oncostatin M receptor; RNA-seq, next-generation RNA-sequencing; SBP-Ag, segmental bronchoprovocation with an allergen; T2, type-2.

Nizar N. Jarjour and Guillaume Lefèvre shared senior authorship.

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tissue OSM correlates with epithelial dysfunction and TSLP expression, but the main source in tissue appears to be the neutrophil [3, 4]. In our present study, we asked whether human blood eosinophils are a source of OSM and analyzed associations between OSM and airway eosinophilia, lung function, and other mediators in asthma.

Blood eosinophils from nine allergic participants were cultured with IL-3 for 20 h. Then, eosinophils were seeded on heat-aggregated IgG for 6 h, which is a well-known model to induce robust degranulation and cytolysis of blood eosinophils [5]. Figure 1A (left panel) shows that in absence of IgG, eosinophils spontaneously released low but detectable amounts of OSM (median [interquartile range; IQR] of 9 pg/mL [4.0, 15.5]) while on IgG (IL3IgG), OSM secretion was 5-fold higher (median IQR of 47 pg/mL [39.5, 55]). Using 3′UTR RNA-seq, we analyzed OSM mRNA expression level in blood eosinophils activated in vitro with IL-3 or eotaxin-1 for 6 h. We found that IL-3 increased OSM expression level (3.5-fold versus no activation) (Figure 1A; right panel). Next, to establish a relationship between airway eosinophilia and OSM in vivo in a type-2 human model, we measured the amount of OSM

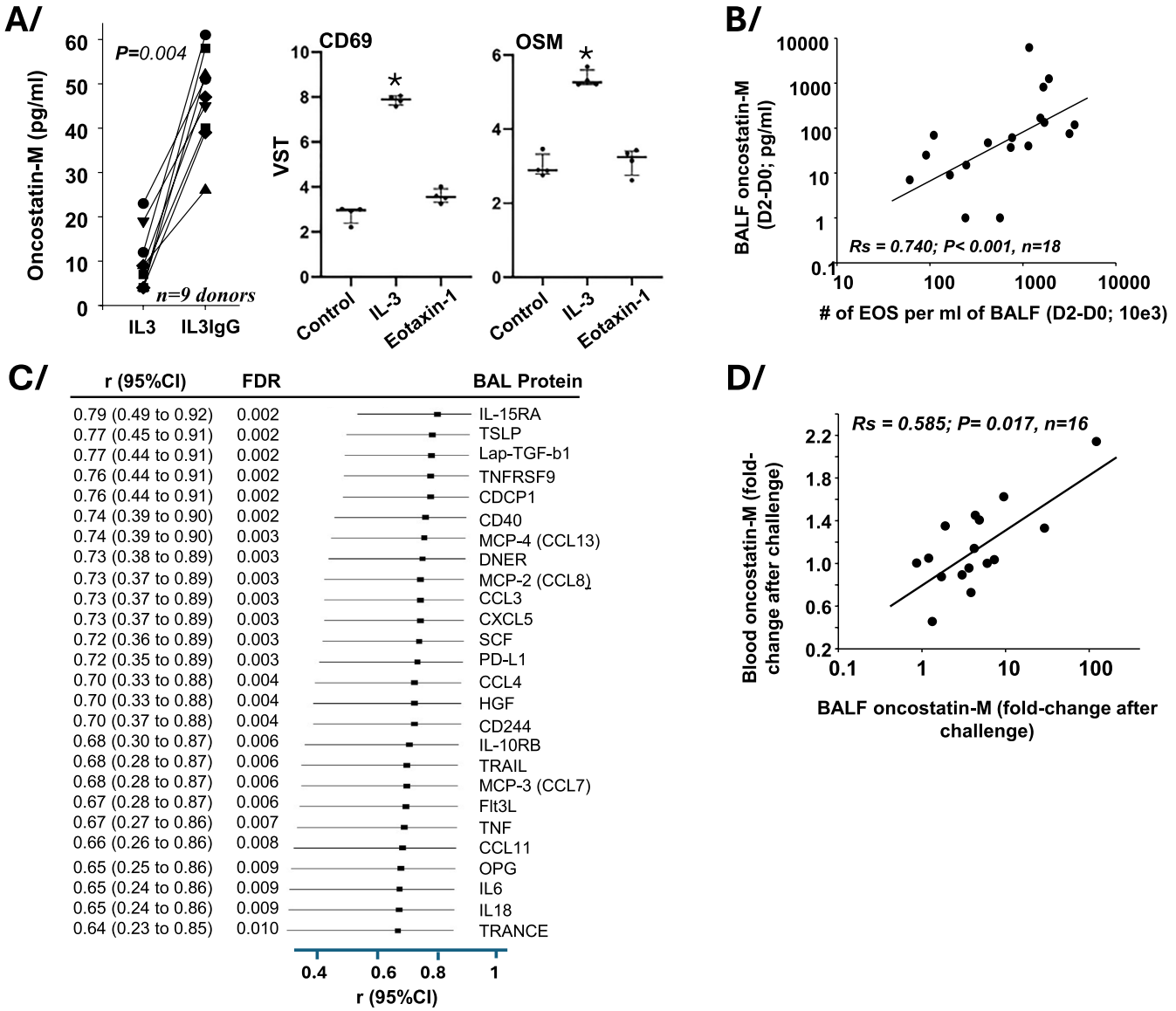

FIGURE 1 | Oncostatin-M is expressed and released by eosinophils, and it is associated with airway eosinophilia and inflammatory mediators after SBP-Ag. (A) (left panel) Blood eosinophils were activated with IL3 (2 ng/mL) for 20 h and then seeded on heat-aggregated IgG (IL3IgG) or no IgG (IL3) for 6 h. Oncostatin-M was quantified in eosinophil cultures by ELISA. (middle and right panel) Blood eosinophils from four healthy donors were activated with IL3 (10 ng/mL) or eotaxin-1 (100 ng/mL) for 6 h. mRNA expression level was determined by 3′UTR RNA-sequencing. Variance stabilizing transformations (VST) for CD69 and OSM are shown. Graphs present medians within 25th and 75th percentiles. *Adjusted $p < 0.05$ compared to Control. (B) BALF oncostatin-M of 18 subjects before (D0) and after SBP-Ag (D2) was quantified by ELISA. Change in BALF oncostatin-M concentration correlated with change in number of BALF eosinophils. (C) Change in BALF oncostatin-M post-vs-pre SBP-Ag was analyzed for correlations with the change of the other detected BALF proteins using the inflammation panel from Olink technology. The 26 most correlated proteins with OSM are shown (FDR ≤ 0.01). (D) Linear fold changes in BALF oncostatin-M correlated with changes in blood oncostatin-M as measured in serum using Olink technology.

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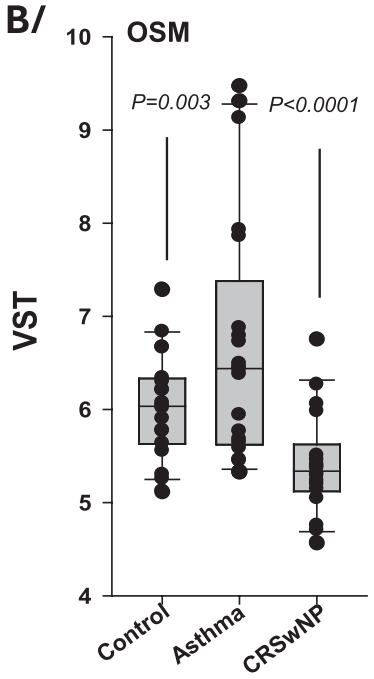
protein in bronchoalveolar lavage (BAL) fluids (BALF) before and 48 h after a segmental bronchoprovocation with an allergen (SBP-Ag) in 18 subjects with mild asthma (previously described in [6]). OSM was detectable in most BALF before SBP-Ag (median IQR of 31 pg/mL [31,45]) and OSM amount increased after the challenge (median IQR of 78 pg/mL [35.5,186.5], $p < 0.0001$). The change in BALF OSM concentration after challenge was correlated with the change in concentration of BALF eosinophils (Figure 1B) and was inversely correlated with the change in lung function as determined using FEV_1 (%*P*) ($r = -0.676$, $p = 0.002$; Table S1). Moreover, to analyze OSM protein in BALF vis-à-vis other well-known mediators of the immune response, 92 mediators were measured in BALF prepared before and after SBP-Ag using Olink Proteomics technology. Changes in BALF OSM strongly correlated with changes in TSLP, Lap-TGF-b1, chemokines, and proinflammatory cytokines (Figure 1C). Furthermore, changes in paired blood OSM amount correlated with changes in BALF OSM (Figure 1D), suggesting an inside-out mechanism with potential systemic impact following SBP-Ag. In Figure 2, we examined whether blood eosinophils displayed higher expression of OSM gene in severe asthma ($n = 21$) compared to healthy individuals ($n = 19$) and patients suffering from CRSwNP ($n = 18$) (Figure 2A). After adjustment for sex, expression level of OSM in isolated blood eosinophils was significantly elevated in severe asthma versus control and CRSwNP (Figure 2B), and OSM levels tended to correlate with two markers for loss of asthma control (ACQ and exacerbations) (Figure 2C).

In conclusion, OSM is a product from activated eosinophils, and its expression is enhanced in eosinophils from patients with uncontrolled severe asthma. Airway OSM levels are associated with poorer lung function and multiple markers of inflammation

A/ Patients' characteristics

	Severe asthma	Healthy controls	CRSwNP
N	21	19	18
Age (years)	47 ± 3.67	40 ± 4.1	51 ± 3
Sex (% female) *	76	53	33
Age at asthma onset	26 ± 4.6		
FEV_1 Predicted (%)	76.5 ± 5.5		
FEV_1/FVC (%)	68 ± 3.1		
FeNO (part per billion)	46 ± 10		
Exacerbations (last 12 months)	7 ± 1.6		
ACQ	2.85 ± 0.22		
Dose ICS_Becl. Equiv. (µg/day)	1043 ± 117 &		419 ± 59
Total IgE (kU/L)	296 ± 112		
Sensitized to ≥1 allergen	11		
Blood eosinophils (per mm^3) #	233 ± 44 (n=19)	125 ± 13	303 ± 76 (n=17)
Sputum eosinophils (%) (n=19)	1.9 ± 1.12		
Sputum neutrophils (%)	34.2 ± 8.75		
Sputum lymphocytes (%)	4.9 ± 1.53		

Mean ± standard error. *Chi-square <0.05 between the 3 groups. # differences between groups (p=0.017; ANOVA followed by Dunn's Method. & *p<0.05* between severe asthma and CRSwNP (Mann-Whitney U test). Abbreviations: ACQ, asthma control questionnaire; Becl. Equiv., beclomethasone equivalent; FeNO : Fractioned exhaled nitric oxide; FEV_1: forced exhaled volume in 1 sec; FVC: forced vital capacity; ICS : inhaled corticosteroids; CRSwNP : chronic rhinosinusitis with nasal polyps



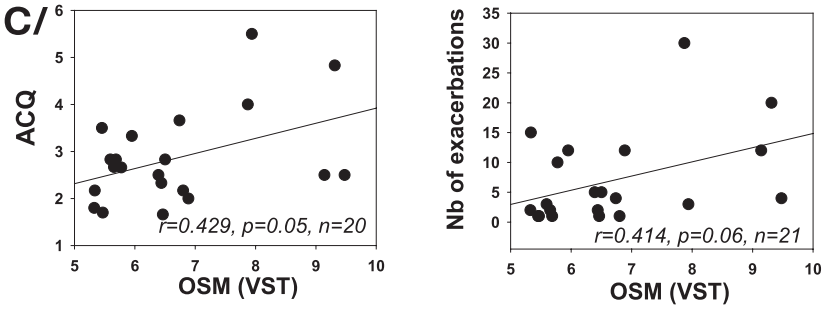


FIGURE 2 | Expression level of OSM in blood eosinophils is increased in severe asthma and it is associated with ACQ and number of exacerbations. Isolated blood eosinophils from 19 healthy controls, 21 patients with severe asthma and 18 with chronic rhinosinusitis with polyps without asthma underwent RNA-sequencing. (A) Participants' characteristics. (B) Isolated blood eosinophils underwent RNA-sequencing and variance stabilizing transformation (VST) and adjustment for sex was applied to the fold changes in expression level between groups. Median OSM level and interquartile range with 75th and 25th percentile is shown. For differences of expression level of genes between asthma patients and the other groups, *p* values adjusted for multiple comparisons were determined for all genes using the FDR procedure (Benjamini–Hochberg) and were reported for OSM. (C) OSM levels in eosinophils from the patients with asthma were analyzed for correlations with ACQ and number (Nb) of exacerbations in the last 12 months (Pearson).

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and remodeling. This study should encourage further investigations on the role of OSM in asthma with the prospect that OSM, its inducer(s) or its downstream signaling becomes a drug target to treat eosinophilic asthma.

Author Contributions

All authors have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; and have been involved in drafting the manuscript or revising it critically for important intellectual content; and have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and they agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of Interest

K. Bernau received funding from the Pulmonary Fibrosis Foundation, by an independent grant from Boehringer Ingelheim Pharmaceuticals Inc. who provided the financial support outside of the submitted work. W. W. Busse reports consulting fees/honoraria from GlaxoSmithKline, Regeneron, Sanofi, and Genentech, and royalties from Elsevier. N. N. Jarjour received research funding from AstraZeneca for extension of the National Institutes of Health–funded severe asthma research program; and received consulting fees over the past 3 years from GlaxoSmithKline, Chiese, and AstraZeneca related to asthma treatment. K. A. Dill-McFarland reports consulting fees from Seattle BioSoftware and EuropaDX related to computational tool development. F. Dezoteux was investigator for clinical trials sponsored by Abbvie, Almirall, Amgen, AstraZeneca, Eli Lilly, Galderma, Leo Pharma, Novartis, Pfizer, and Sanofi-Regeneron; received consulting fees by AbbVie, Almirall, Eli Lilly, Galderma, Leo Pharma, Novartis, Pfizer, Sanofi-Regeneron, and UCB. D. Staumont-Sallé received funding from AstraZeneca for a research study in DRESS syndrome; was investigator for clinical trials sponsored by Abbvie, Almirall, Amgen, AstraZeneca, Eli Lilly, Galderma, Leo Pharma, Novartis, Pfizer, and Sanofi-Regeneron; received consulting fees by AbbVie, Almirall, AstraZeneca, Eli Lilly, Galderma, GSK, Leo Pharma, Novartis, Pfizer, Sanofi-Regeneron, and UCB. C. Chenivesse declares research grants from AstraZeneca, GlaxoSmithKlein, Santelys, and Novartis, personal fees from ALK-Abello, AstraZeneca, Boehringer Ingelheim, Chiesi, Sanofi, and GlaxoSmithKlein and congress support from AstraZeneca, Boehringer Ingelheim, Chiesi, and Novartis. G. Lefèvre received consulting fees, personal fees for advisory boards or meetings, and research fundings from AstraZeneca and GSK. These relationships with pharmaceutical companies are not relevant to the current study. M. W. Johansson received funding from Hoffmann-La Roche, outside of the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

Data Availability Statement

All the data used in this manuscript are available to the public.

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