

The dendritic cell high-affinity IgE receptor is overexpressed in both asthma and severe COPD

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Summary

Background The reduction of asthma exacerbations following omalizumab treatment has been related to the suppression of the high-affinity IgE receptor (FcεRI) on plasmacytoid dendritic cells (DCs). However, the FcεRI expression on DCs in chronic obstructive pulmonary disease (COPD) is unknown.

Objective To compare FcεRI expression on DCs in COPD with patients with allergic asthma and healthy controls, and to relate the findings to clinical parameters, blood eosinophil concentrations and serum immunoglobulin E (IgE) concentrations.

Methods Using four-colour flow cytometry, FcεRI expression on blood myeloid DCs and plasmacytoid DCs was analyzed in 64 patients with COPD, 20 patients with allergic asthma, 41 asymptomatic never smokers and 21 asymptomatic current smokers.

Results As compared with never smokers, current smokers displayed an increased expression of the FcεRI on myeloid and plasmacytoid DCs. In patients with COPD, the expression of the FcεRI on plasmacytoid DCs, but not myeloid DCs, increased from spirometric GOLD stage 2 to GOLD stage 4, and was correlated with several lung function parameters. Patients with severe COPD and patients with allergic asthma displayed a similar FcεRI overexpression on plasmacytoid DCs. In all groups, there was a positive correlation between total IgE serum concentrations and the FcεRI expression on plasmacytoid DCs.

Conclusions and Clinical Relevance Severe COPD and allergic asthma are characterized by a similar overexpression of the high-affinity IgE receptor on plasmacytoid DCs. In view of the effect of anti-IgE on exacerbations in asthma, trials investigating the effect of anti-IgE on exacerbations in severe COPD appear to be warranted.

Keywords asthma, COPD, dendritic cell, immunoglobulin E, flow cytometry

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Introduction

Anti-IgE treatment in asthma was initially based on the concept that the removal of circulating IgE would reduce allergen-induced mast cell degranulation and subsequently lead to a reduction of allergic airway inflammation. This concept was challenged by evidence showing that omalizumab is equally effective in patients with intrinsic asthma ('non-allergic' patients) [1]. One hypothesis suggested that patients labelled as 'non-allergic' (based on negative skin prick tests and/or negative specific IgE measurements) might in fact be allergic to unrecognized allergens and that anti-IgE treatment would, therefore, still be beneficial [1].

Another hypothesis, however, suggests that the effects of omalizumab are partly independent of the

presence of allergies [1]. Plasmacytoid dendritic cells (pDCs) are key players both in innate immune defences against (predominantly viral) infections and in allergic immune responses [2–4]. Crosslinking of IgE bound to the high-affinity IgE receptor (also known as FcεRI) on pDCs suppresses the antiviral activity of pDCs, suggesting that IgE crosslinking increases the risk of virus-induced asthma exacerbations [5–7]. Patients with asthma display an increased expression of FcεRI on blood pDCs, and this expression is positively correlated with total IgE serum concentrations [5, 8, 9]. In omalizumab-treated patients, the reduction of asthma exacerbations was explained by a downregulation of the high-affinity IgE receptor on pDCs [10–12]. Thus, there is currently a paradigm shift from the concept of a solely anti-allergic, mast cell-driven effect to the

concept of an additional antiviral, DC-driven effect of anti-IgE antibodies in asthma [13].

Although exacerbations have a major impact on morbidity and mortality in COPD [14], there is currently no information on the role and expression of the FcεRI on pDCs in patients with COPD. In a series of studies, we have shown characteristics of DCs in the airways and in peripheral blood of asymptomatic smokers and of patients with COPD [15–18]. COPD is characterized by an imbalanced expression of DC co-stimulatory molecules (OX40L and PD-L1) [17]. We hypothesized that DCs of patients with COPD might also display an altered expression of the high-affinity IgE receptor. It was the aim of the current study, therefore, to elucidate the expression of the FcεRI on blood DCs of patients with COPD for the first time, and to relate this expression to serum IgE concentrations, blood eosinophil counts and disease severity. Using an established flow cytometric method to analyse human blood DCs [17, 19], we compared the expression of the FcεRI on blood DCs of patients with COPD of different severity with 3 control groups: asymptomatic never smokers with normal lung function, asymptomatic current smokers with normal lung function and patients with allergic asthma.

Methods

Participants

Patients with allergic asthma were recruited in an outpatient clinic in Rostock (Germany). Inclusion criteria for patients with allergic asthma were as follows: (i) doctor's diagnosis of allergic asthma, (ii) documented airway hyper-responsiveness (demonstrated by methacholine or histamine provocation) and/or reversibility of bronchial obstruction (increase of the forced expiratory volume in the first second, FEV₁, by at least 15% and at least 200 mL after inhalation of a short-acting beta-agonist) and (iii) sensitization to a common aeroallergen. Exclusion criteria for patients with allergic asthma were as follows: (i) any malignant diseases and (ii) any signs of an exacerbation or any treatment with antibiotics or systemic corticosteroids within the last 4 weeks prior to enrolment. The groups of never smokers and current smokers with normal lung function were recruited using public notices, with the following inclusion criteria: (i) no history of asthma or other chronic respiratory diseases and (ii) no history of smoking and no exposure to smoking partners or relatives at home (never smokers) or a self-reported smoking history of at least 5 pack years and current smoking of at least 15 cigarettes per day (current smokers). For both control groups, exclusion criteria were as follows: (i) presence of any malignant or chronic inflammatory diseases and (ii) any infection or treatment with antibiotics

within the last 4 weeks prior to enrolment. Patients with stable COPD were recruited at the University Hospital of Rostock (Germany). Inclusion criteria for patients with COPD were as follows: (i) doctor's diagnosis of COPD, (ii) self-reported smoking history of at least 5 pack years and (iii) a FEV₁/FVC ratio < 70% after inhalation of a short-acting beta-agonist. Exclusion criteria for patients with COPD were as follows: (i) any history of asthma, (ii) any malignant diseases and (iii) any signs of an exacerbation or any treatment with antibiotics or systemic corticosteroids within the last 4 weeks prior to enrolment. The study was approved by the local ethics committee of the Ärztekammer Mecklenburg-Vorpommern, Rostock (Germany). All participants gave their written informed consent.

Study design and flow cytometry

Following detailed history taking, body plethysmography was performed and the diffusion capacity (DLCO) was measured (Masterscreen, Jaeger, Carefusion, Hoechst, Germany). Afterwards, peripheral blood was taken for laboratory analyses and for the analysis of blood DCs. Blood DCs were analyzed as described [17, 19]. Briefly, freshly collected EDTA blood was incubated with the respective antibodies for 20 min. Afterwards, FACS lysing solution (BD Biosciences, Heidelberg, Germany) was added for another 10 min. Cells were centrifuged for 5 min (400 g) and washed with phosphate-buffered saline (PBS) containing 2% foetal calf serum and 0.1% NaN₃. Finally, cells were resuspended in PBS and analyzed by flow cytometry using a FACS Calibur and Cell Quest Pro software (both BD Biosciences, Heidelberg, Germany). The following antibodies were used: FITC-labelled Lineage cocktail containing anti-CD3 (clone SK7), anti-CD14 (clone MφP9), anti-CD16 (clone 3G8), anti-CD19 (clone SJ25C1), anti-CD20 (clone L27), anti-CD56 (clone NCAM 16.2) as well as anti-CD11c PE (clone S-HCL-3), anti-CD123 PE (clone 9F5), anti-HLA-DR PerCP (clone L243) all from BD Biosciences (Heidelberg, Germany), anti-FcεRIα APC (eBioscience, Frankfurt, Germany) and mouse IgG2b APC isotype control (clone MPC-11, BioLegend, Fell, Germany). Among blood cells negative/dim for lineage markers (CD3, CD14, CD16, CD19, CD20 and CD56), myeloid DCs (mDCs) were defined as CD11c⁺HLA-DR⁺lin^{neg/dim} cells and pDCs as CD123⁺HLA-DR⁺lin^{neg/dim} cells, as described [17, 19] and shown in Fig. S1 (online supplement). The expression of the high-affinity IgE receptor (FcεRI) on DCs was quantified in histogram plots using an isotype control antibody to discriminate between specific and non-specific staining (Fig. S2, online supplement). Due to the expression of FcεRI on the whole population of mDCs, FcεRI expression on mDCs was quantified as the median fluorescence intensity (MFI)

and calculated as net MFI (MFI FcεRI antibody – MFI control antibody). In contrast, FcεRI expression was confined to subpopulations of the pDCs and, therefore, quantified as the percentage of FcεRI-positive pDCs (Fig. S2, online supplement).

Measurement of IgE in human serum

Total IgE concentrations in human serum were measured using the UniCAP 100 System (Thermo Scientific, Braunschweig, Germany) as described by the manufacturer. The sensitivity of the assay is 0.2 kU/L.

Statistical analysis

Statistical analysis was performed using SPSS Statistics (Version 20, IBM, Armonk, NY, USA). Most parameters were not normally distributed, parameters were expressed, therefore, as medians (minimum – maximum). The Mann–Whitney U-test for unrelated samples was used for direct comparisons of the parameters between specific groups. General differences in the expression of FcεRI between the groups were analyzed using the Kruskal–Wallis test. The Jonckheere–Terpstra test was used for the analysis of trends in FcεRI expression. Correlation analyses were performed using Spearman's correlation coefficient. Probability values of $P < 0.05$ were regarded as significant. Box plots display the median (line within the box), interquartile range (edges of the box) and extremes (vertical lines). Significant differences between the groups are marked with the P -value.

Results

Characteristics of the participants

Forty-one asymptomatic never smokers, 21 asymptomatic current smokers, 20 patients with allergic asthma and 64 patients with the diagnosis of COPD (26 patients in spirometric GOLD stage 2, 29 patients in spirometric GOLD stage 3 and 8 patients in spirometric GOLD stage 4) were included in the study. Characteristics of the participants are detailed in Table 1. The group of patients with asthma was significantly younger (median age: 24 years) than the groups of asymptomatic never smokers, asymptomatic current smokers and patients with COPD (median ages: 57 – 69 years). There was no difference in the smoking history (number of pack years) between asymptomatic current smokers and patients with COPD (Table 1). In the group of patients with COPD, only 3 patients (4.8% of the total group of 63 patients with COPD) had self-reported allergies: 1 patient reported allergies against wasp venom and house dust mite, 1 patient reported

Table 1. Characteristics of the participants

	Never smoker <i>n</i> = 41	Smoker <i>n</i> = 21	COPD GOLD II <i>n</i> = 26	COPD GOLD III <i>n</i> = 29	COPD GOLD IV <i>n</i> = 8	Asthma <i>n</i> = 20
Age (years)	69.0 [§] [50...85]	61.0 [§] [51...75]	65.5 [§] [40...83]	65.0 [§] [48...85]	57.0 [§] [50...68]	24.0 [§] [19...67]
Gender (m/w)	26/15	13/8	17/9	19/10	5/3	10/10
Body mass index (kg/m ²)	24.7 [20.7...32.3]	29.4 [§] [18.3...38.8]	28.8 [§] [20.0...40.0]	26.0 [15.0...41.0]	23.5 [16.0...31.0]	24.3 [21.1...30.0]
Pack years	0 [§] [0...0]	39 [§] [23...69]	37 [§] [10...88]	35 [§] [5...70]	35 [§] [20...80]	0 [§] [0...15]
FEV ₁ % pred. (%)	107.2 [84.2...134.3]	97.8 [§] [65.9...124.3]	61.1 [§] [50.3...78.7]	39.3 [§] [30.0...48.1]	22.6 [§] [16.1...29.7]	105.1 [28.9...119.8]
FVC % pred. (%)	106.3 [60.5...132.3]	94.7 [§] [57.2...132.0]	84.5 [§] [60.8...109.8]	68.0 [§] [37.0...104.0]	49.3 [§] [45.3...78.5]	102.0 [38.7...125.7]
FEV ₁ % FVC (%)	80.3 [§] [70.8...91.1]	79.6 [70.7...94.5]	58.5 [§] [43.2...70.0]	47.1 [§] [36.9...64.8]	41.3 [§] [25.7...56.5]	84.0 [§] [62.4...97.1]
MEF ₅₀ % pred. (%)	94.3 [37.3...162.7]	75.4 [§] [29.3...123.0]	23.6 [§] [9.9...38.7]	11.0 [§] [5.8...25.8]	7.9 [§] [5.2...9.9]	88.5 [11.8...168.6]

Shown are median values [minimum ... maximum] of each parameter in each group and in the COPD subgroups (spirometric GOLD stages II, III and IV).

[§] $P < 0.05$ compared with the group of never smokers.

[§] $P < 0.05$ compared with the group of patients with allergic asthma.

FEV₁, Forced expiratory volume in the first one-second; FEV₁/FVC, ratio of the FEV₁ to the forced vital capacity; MEF₅₀, maximum expiratory flow when 50% of the FVC is exhaled.

allergies against house dust mite and animal hair and 1 patient an allergy against cats. Patients with COPD had significantly worse lung function parameters than the 3 control groups of never smokers, current smokers and patients with asthma (Table 1). None of the participants in the control groups of never smokers or current smokers was treated with inhaled medications. In the group of patients with COPD ($n = 63$), 3 patients were treated with reliever therapy (as needed) only, 1 patient with a long-acting muscarinic antagonist (LAMA) monotherapy, 5 patients with a long-acting beta-agonist (LABA) monotherapy, 18 patients with a LAMA/LABA combination therapy, 5 patients with a fixed combination of a LABA and an inhaled corticosteroid (ICS) and 31 patients with a triple therapy (LAMA/LABA/ICS). In the group of patients with asthma, 10 patients were treated with reliever therapy (as needed) only, 1 patient with an ICS monotherapy and 9 patients with a ICS/LABA fixed combination.

Concentrations of IgE, eosinophils and DCs in peripheral blood

In contrast to asymptomatic smokers and patients with COPD, patients with allergic asthma displayed significantly elevated total IgE serum concentrations and blood eosinophil concentrations, as compared with asymptomatic never smokers (Table 2). The concentrations of pDCs in peripheral blood were significantly elevated in patients with allergic asthma (but not in current smokers or patients with COPD), as compared with never smokers (Table 2). Percentages of mDCs in peripheral blood were significantly lower in the 3 COPD subgroups and in current smokers (but not in patients with allergic asthma), as compared with never smokers. However, significantly lower blood mDC concentrations were found only in patients with spirometric GOLD stage 4 and in current smokers (Table 2).

Expression of the high-affinity IgE receptor on blood DCs

Asymptomatic current smokers displayed a significantly increased expression of the FcεRI on blood pDCs and mDCs, as compared with asymptomatic never smokers and patients with COPD in spirometric GOLD stage 2 (Figs 1 and 2). The analysis of COPD subgroups (spirometric GOLD stages 2, 3 and 4) using the Kruskal–Wallis test revealed significant differences between the COPD subgroups for FcεRI expression on pDCs ($P = 0.007$), but not mDCs ($P = 0.068$ for the percentage of FcεRI on mDCs and $P = 0.210$ for FcεRI MFI on mDCs). Direct comparisons of the COPD subgroups using the Mann–Whitney U-test revealed that the expression of the FcεRI on blood pDCs, but not mDCs, increased significantly with increasing spirometric GOLD stages (Figs 1 and 2).

Table 2. Blood parameters of the participants

	Never smoker $n = 41$	Current smoker $n = 21$	COPD GOLD II $n = 26$	COPD GOLD III $n = 29$	COPD GOLD IV $n = 8$	Allergic asthma $n = 20$
Eosinophils (% of leucocytes)	2.1 [§] [0.5...11.3]	2.1 [§] [0.0...5.1]	2.4 [§] [0.0...7.3]	2.2 [§] [0.30...6.9]	1.7 [§] [0.2...7.2]	4.8 [§] [0.8...10.6]
Eosinophils (10^3 /mL blood)	150 [§] [31...560]	142 [§] [0...363]	176 [§] [0...638]	205 [35...611]	168 [19...648]	259 [§] [77...750]
Serum IgE (kU/L)	28.2 [§] [2...366]	37.4 [6...1776]	13.7 [§] [3...877]	40.2 [5...499]	84.7 [7...1355]	97.8 [§] [2...1114]
pDC (% of leucocytes)	0.08 [§] [0.04...0.25]	0.08 [§] [0.02...0.19]	0.095 [§] [0.02...0.19]	0.09 [§] [0.02...0.16]	0.07 [§] [0.02...0.22]	0.16 [§] [0.04...0.43]
pDC (10^3 /mL blood)	5.5 [§] [2.6...15.4]	7.0 [1.7...19.4]	6.0 [§] [1.5...16.9]	7.1 [2.3...15.5]	6.1 [2.0...15.9]	8.0 [§] [3.7...20.9]
mDC (% of leucocytes)	0.23 [0.09...0.54]	0.14 [§] [0.05...0.27]	0.17 [§] [0.05...0.37]	0.16 [§] [0.03...0.40]	0.10 [§] [0.04...0.21]	0.27 [0.11...0.52]
mDC (10^3 /mL blood)	14.2 [5.0...51.6]	11.0 [§] [3.5...29.2]	11.1 [§] [3.9...30.4]	11.7 [§] [3.5...31.2]	9.0 [§] [3.7...18.9]	16.1 [8.8...33.5]

Shown are median values [minimum ... maximum] of each parameter in each group and in the COPD subgroups.

[§] $P < 0.05$ compared with the group of never smokers.

[§] $P < 0.05$ compared with the group of patients with allergic asthma.

IgE, Immunoglobulin E; pDCs, plasmacytoid dendritic cells; mDCs, myeloid dendritic cells.

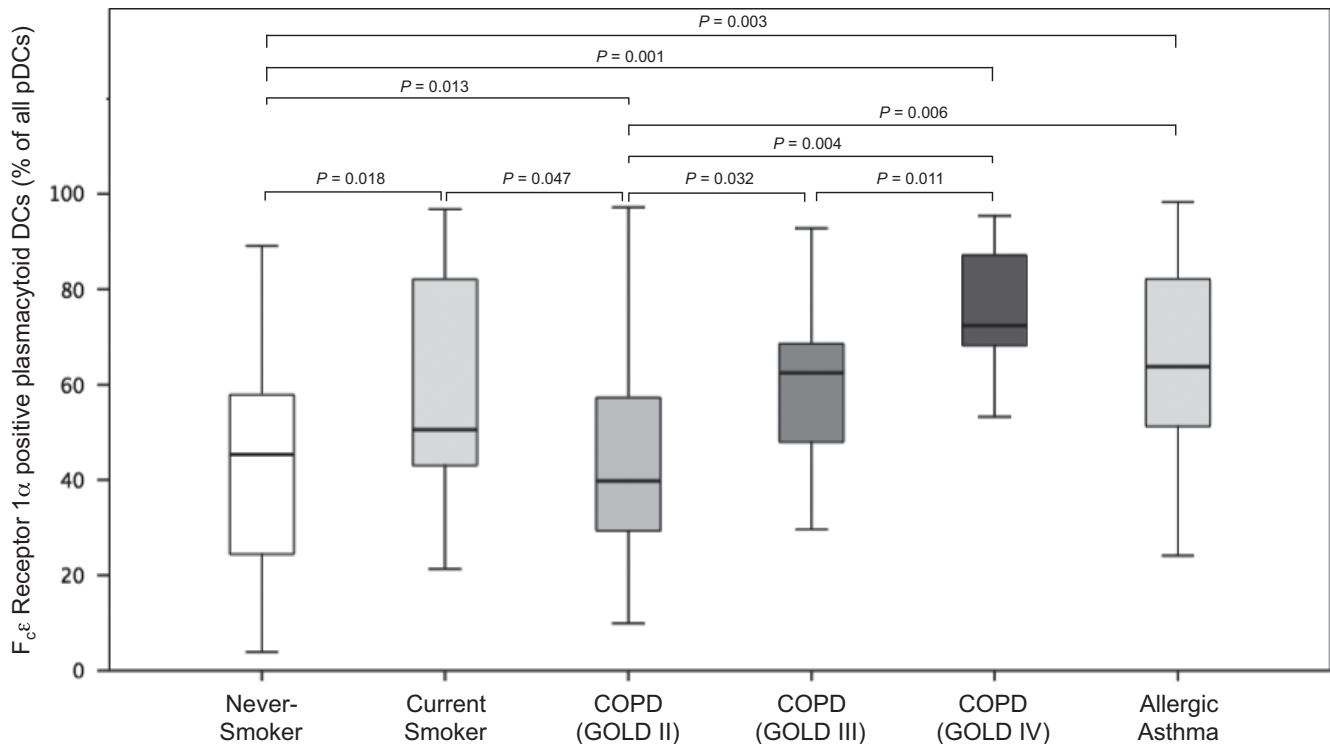


Fig. 1. Expression of the high-affinity IgE receptor on blood pDCs. Box plots show the expression (% positive pDCs) of the FcεRI on blood pDCs of 41 never smokers with normal lung function (Never Smoker), 21 current smokers with normal lung function (Current Smoker), 26 patients with COPD in spirometric GOLD stage II (COPD GOLD II), 29 patients with COPD in spirometric GOLD stage III (COPD GOLD III), 8 patients with COPD in spirometric GOLD stage IV (COPD GOLD IV) and 20 patients with allergic asthma (Allergic asthma). Box plots display the median (line within the box), interquartile range (edges of the box) and extremes (vertical lines). Significant differences between the groups are marked with the exact *P*-value.

The Jonckheere–Terpstra test confirmed that there was a trend to increasing FcεRI expression on pDCs ($P = 0.002$), but not on mDCs ($P = 0.054$ for the percentage of FcεRI on mDCs and $P = 0.078$ for FcεRI MFI on mDCs), with increasing COPD severity. The FcεRI overexpression on pDCs did not significantly differ between patients with allergic asthma and patients with COPD in spirometric GOLD stages 3 or 4 (Fig. 1).

Association with clinical parameters, blood eosinophils, and serum IgE

The expression of the FcεRI on pDCs (but not mDCs) was significantly negatively correlated with the FEV₁ (Fig. 3a), the MEF₅₀ (Fig. 3b) and the FVC (Fig. 3c) in patients with COPD. In contrast, the association with the smoking history (number of pack years) of the patients was not significant (Fig. 3d). There were no significant correlations between total IgE concentrations in serum and the FEV₁ in the total group of patients with COPD ($r = -0.142$, $P = 0.266$, Fig. S3, online supplement), and in the subgroups of patients with spirometric GOLD stage II ($r = -0.112$, $P = 0.594$), spirometric GOLD stage III ($r = 0.199$, $P = 0.302$) and spirometric GOLD stage IV ($r = 0.381$, $P = 0.352$) (data

not shown). There was no significant correlation between blood eosinophil concentrations and the expression of the FcεRI on pDCs in never smokers ($r = 0.10$, $P = 0.535$), current smokers ($r = 0.430$, $P = 0.052$), patients with COPD ($r = 0.160$, $P = 0.215$) and patients with asthma ($r = 0.075$, $P = 0.766$) (data not shown). In contrast, there was a significant correlation between total serum IgE concentrations and the expression of the FcεRI on pDCs and mDCs in all examined groups (Figs S4 and S5, online supplement).

Discussion

This is the first report elucidating the expression of the high-affinity IgE receptor (FcεRI) on pDCs in COPD. We demonstrate, for the first time, that the FcεRI is overexpressed on pDCs in severe COPD, in a similar fashion as previously observed on pDCs in asthma [5, 8, 9]. In addition, this study reveals that the expression of FcεRI on pDCs (but not total serum IgE) is correlated with lung function impairment in COPD. Thus, our data suggest that FcεRI expression on pDCs might not only play a role in asthma, but also in severe COPD.

The presence of airway wall lymph follicles correlates with airway obstruction in COPD [20] and represents a

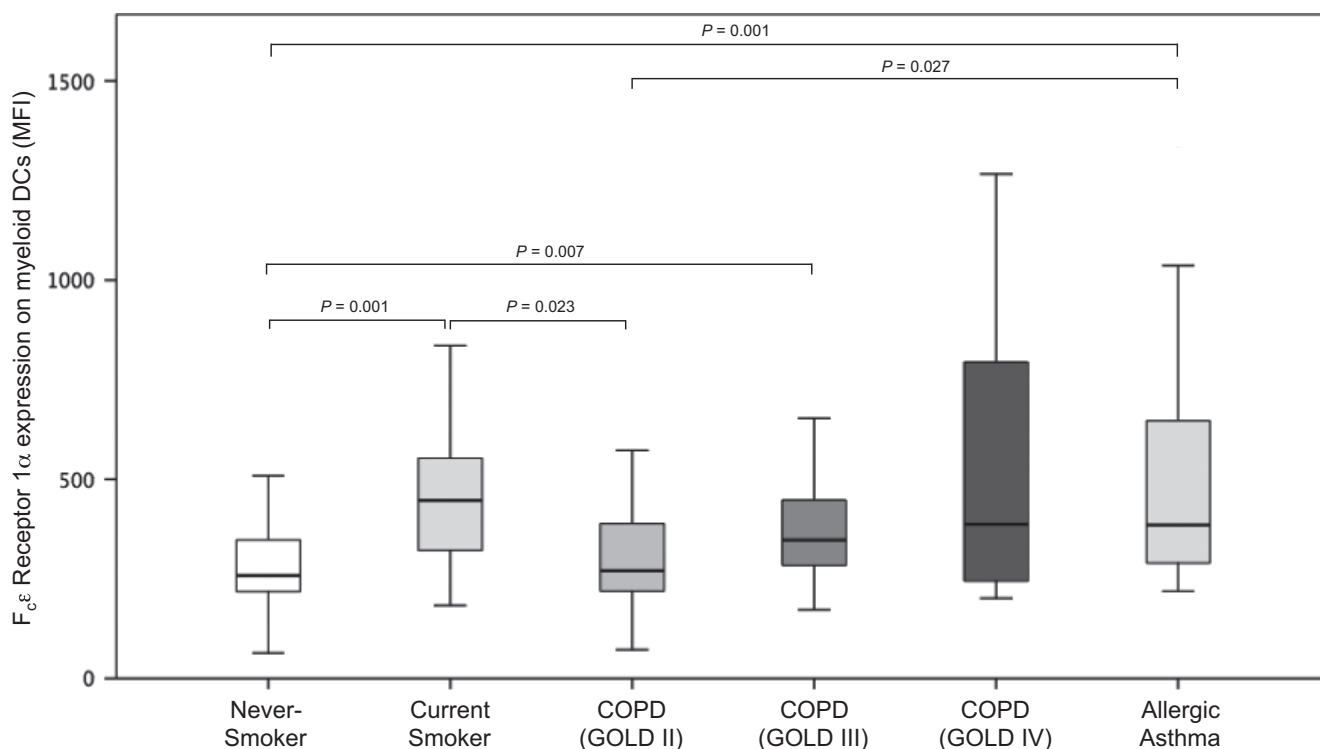


Fig. 2. Expression of the high-affinity IgE receptor on blood mDCs. Box plots show the expression (median fluorescence intensity, MFI) of the FcεRI on blood mDCs of 41 never smokers with normal lung function (Never Smoker), 21 current smokers with normal lung function (Current Smoker), 26 patients with COPD in spirometric GOLD stage II (COPD GOLD II), 29 patients with COPD in spirometric GOLD stage III (COPD GOLD III), 8 patients with COPD in spirometric GOLD stage IV (COPD GOLD IV) and 20 patients with allergic asthma (Allergic asthma). Box plots display the median (line within the box), interquartile range (edges of the box) and extremes (vertical lines). Significant differences between the groups are marked with the exact *P*-value.

key element in the immunopathology of the disease [21]. Local DC accumulation is a major driver of lymph follicle formation in COPD airways and has, therefore, been implicated in the pathogenesis of COPD [21–23]. Specific chemokines and chemokine receptors contribute to the accumulation and activation of DCs in the airway wall of patients with COPD [16, 22]. The imbalance of DC co-stimulatory molecules appears to have additional proinflammatory effects in this condition [17]. However, the expression and role of the high-affinity IgE receptor on DCs in COPD is unknown. The present study demonstrates, for the first time, that severe COPD ($FEV_1 < 50\%$ predicted), but not mild to moderate COPD ($FEV_1 > 50\%$ predicted), is characterized by an overexpression of FcεRI on pDCs which is similar to the overexpression found in allergic asthma. As there is no evidence that the FcεRI expression on pDCs is affected by age [24], it is unlikely that the results were affected by the different median ages of the groups. Thus, the data reveal a hitherto unknown immunological similarity between asthma and severe COPD. The immunological regulation and pathophysiological role of enhanced FcεRI expression on pDCs in severe COPD is currently unknown. It might be specu-

lated that an increased FcεRI expression on pDCs could simply be the result of increased serum IgE concentrations in COPD (there were associations between serum IgE concentrations and pDC FcεRI expression in all groups). However, in contrast to the pDC FcεRI expression, we did not find a correlation between serum IgE and COPD severity. Thus, a simple immunological link between serum IgE and pDC FcεRI expression does not appear to explain the findings. It is, therefore, conceivable that there are specific similarities in the inflammatory response between asthma and severe COPD leading to a similar upregulation of this receptor on pDCs. This hypothesis is supported by studies demonstrating that patients with COPD can show features of a Th2-driven inflammation [25, 26] and can benefit from treatment with cytokine inhibitors designed for patients with asthma [27].

There is currently no information on the expression of the FcεRI on pDCs in the airways or lung parenchyma of patients with COPD. In contrast, the study by Greer et al. analyzed FcεRI expression on pulmonary myeloid DCs of patients with COPD [28]. This study had several limitations (only the BDCA-1-positive subpopulation of myeloid DCs was analyzed; the digestion and

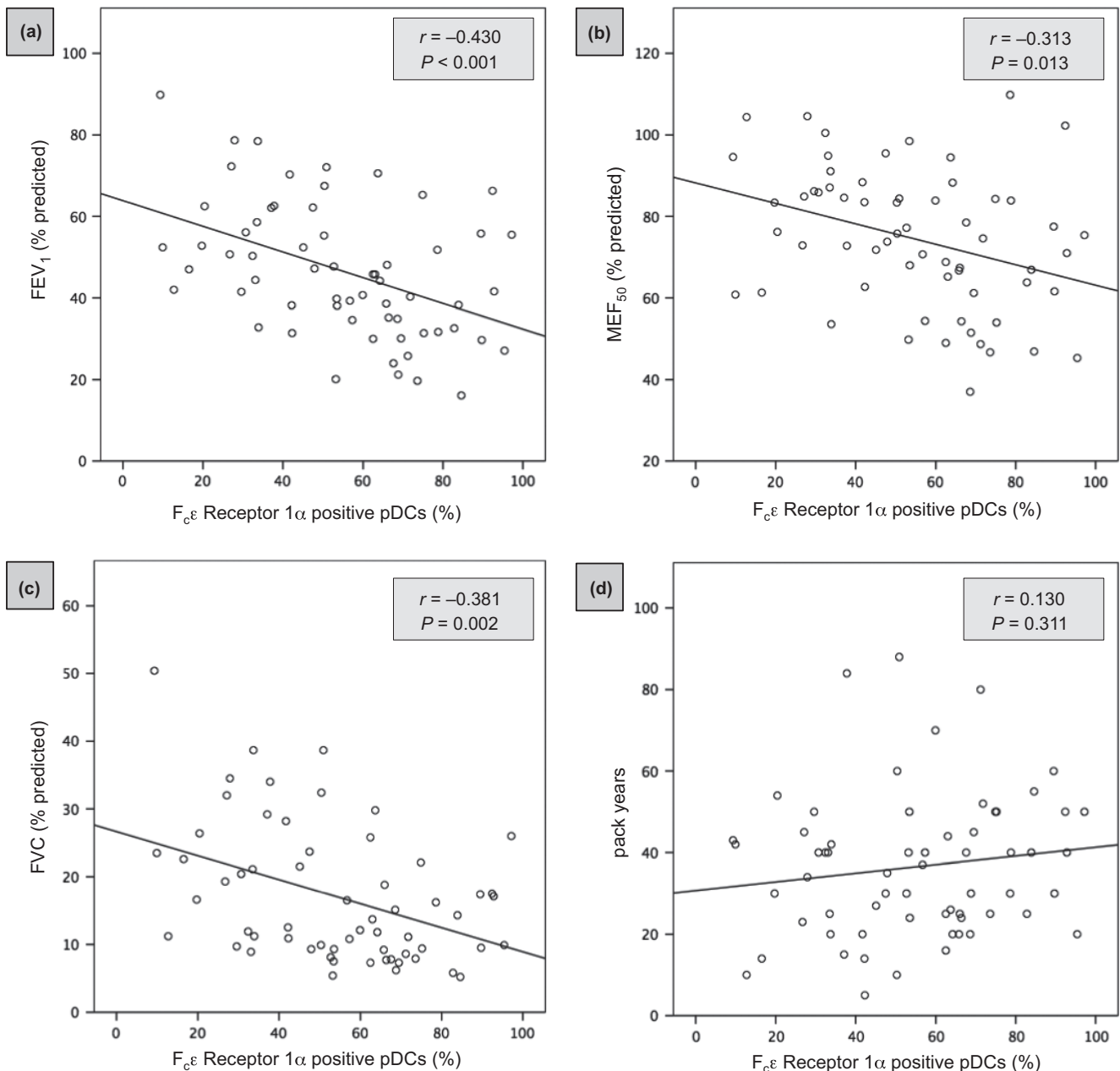


Fig. 3. Correlation of the pDC FcεRI expression with clinical parameters. Shown are correlations of the percentage of FcεRI-positive pDCs in peripheral blood with the forced expiratory capacity (FEV₁) (a), the maximum expiratory flow at 50% of the vital capacity (MEF₅₀) (b), the forced vital capacity (FVC) (c) and the number of pack years (d) in the group of 64 patients with COPD. The Spearman correlation coefficient (r) and the P -value (P) are shown for each correlation.

mechanical dispersion of pulmonary tissues for flow cytometric analyses are prone to DC artefacts; only 7 patients with COPD were examined) and did not directly compare myeloid DC FcεRI expression between patients with COPD and patients with asthma [28]. However, in agreement with our findings, this study showed that the trend to an increase in the FcεRI expression on myeloid DCs in patients with COPD, as compared with healthy controls, was not significant [28]. Thus, it appears that

FcεRI overexpression in severe COPD is mainly a phenomenon found in pDCs, rather than in mDCs. Further studies analysing the FcεRI expression on pulmonary DCs of patients with COPD are, therefore, needed to further elucidate this issue.

It is well established that patients with asthma display an increased expression of the high-affinity IgE receptor on pDCs and that this expression is correlated with total IgE serum concentrations [5, 8–11]. Ran-

domized controlled trials showed that the anti-IgE antibody omalizumab strongly reduces the FcεRI expression on pDCs in patients with severe allergic asthma [10], in patients with severe intrinsic asthma [11] and patients with allergic rhinitis [12], suggesting that this effect is independent of the presence of allergies or a specific disease. Indeed, FcεRI expression on pDCs appears to be independent of an allergic sensitization and independent of the age in human subjects [24]. Experimental studies revealed that crosslinking of IgE bound to the FcεRI on pDC suppresses the antiviral activity of pDCs [5–7]. Therefore, the omalizumab-induced downregulation of the FcεRI on pDCs may augment antiviral immune responses in asthma, resulting in fewer exacerbations [1]. This is supported by the observation that indeed the reduction of exacerbations appears to be the major clinical effect of omalizumab in severe asthma [13, 29] which can be observed both in patients with allergies and without allergies [1]. Although a reduction of exacerbations is a major treatment goal in COPD, especially in patients with severe disease [14], information on the FcεRI expression on pDCs in COPD has been lacking. Our study shows that the overexpression of this pDC receptor is similar in patients with asthma and patients with severe COPD. Thus, our data suggest that FcεRI might also be a therapeutic target to reduce COPD exacerbations. Further clinical and experimental studies and possibly trials with anti-IgE antibodies (such as omalizumab) are, therefore, warranted to explore whether a FcεRI downregulation on pDCs influences antiviral immune responses and exacerbation rates in COPD.

The analysis of total IgE concentrations in serum did not reveal significant differences between the COPD subgroups and asymptomatic controls. In addition, we did not find a correlation between total serum IgE and lung function in patients with COPD. This is in line with the limited literature on total serum IgE in COPD showing no clear relationship between disease severity and total serum IgE in COPD [30–32]. In contrast, we found a significant correlation of total serum IgE with the FcεRI expression on pDCs. This relationship was not

only present in patients with allergic asthma (in accordance with the literature [5, 8, 9]), but also in patients with COPD and in the control groups suggesting that the close association between serum IgE and the FcεRI on pDCs is a general feature in humans. This finding further supports the idea that anti-IgE treatment might impact on the FcεRI expression of pDCs and consequently on the function of pDCs in COPD. Thus, strategies targeting IgE might indeed be a promising option to modify DC function and clinical outcomes in selected patients with severe COPD.

Taken together, this study demonstrates, for the first time, that severe COPD is characterized by an overexpression of the high-affinity IgE receptor on pDCs, thus revealing a hitherto unknown immunological similarity between asthma and severe COPD. Therapeutic strategies targeting the expression of this pDC receptor might, therefore, not only be effective in patients with asthma, but also in selected patients with severe COPD.

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Author contributions

PS, JCV and ML designed and supervised the study, analyzed the data and wrote the manuscript draft; AB and MU recruited and characterized the participants, obtained the blood samples and helped to perform the flow cytometric measurements; KB and KG planned and performed the flow cytometric measurements and analyses.

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Conflict of interest

All authors declare that they have no conflict of interests related to the submitted manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Gating strategy.

Figure S2. Histogram plots for the analysis of FcεRI expression on DCs.

Figure S3. Correlation of the FEV₁ with serum IgE in patients with COPD.

Figure S4. Correlation of the FcεRI expression on pDCs with Serum IgE.

Figure S5. Correlation of the FcεRI expression on mDCs with Serum IgE.