

# Airway Structural Changes in Asthma

Subjects: Pathology

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## Definition

Increased airway wall thickness and remodeling of bronchial mucosa are characteristic of asthma and may arise from altered integrin signaling on airway cells. Here, we analyzed the expression of  $\beta$ 1-subfamily integrins on blood and airway cells (flow cytometry), inflammatory biomarkers in serum and bronchoalveolar lavage, reticular basement membrane (RBM) thickness and collagen deposits in the mucosa (histology), and airway geometry (CT-imaging) in 92 asthma patients (persistent airflow limitation subtype:  $n=47$ ) and 36 controls. Persistent airflow limitation was associated with type-2 inflammation, elevated soluble  $\alpha$ 2 integrin chain, and changes in the bronchial wall geometry. Both subtypes of asthma showed thicker RBM than control, but collagen deposition and epithelial  $\alpha$ 1 and  $\alpha$ 2 integrins staining were similar. Type-I collagen accumulation and RBM thickness were inversely related to the epithelial expression of the  $\alpha$ 2 integrin chain. Expression of  $\alpha$ 2 $\beta$ 1 integrin on T-cells and eosinophils was not altered in asthma. Collagen I deposits were, however, more abundant in patients with lower  $\alpha$ 2 $\beta$ 1 integrin on blood and airway CD8+ T-cells. Thicker airway walls in CT were associated with lower  $\alpha$ 2 integrin chain on blood CD4+ T-cells and airway eosinophils. Our data suggest that  $\alpha$ 2 $\beta$ 1 integrin on inflammatory and epithelial cells may protect against airway remodeling advancement in asthma.

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## 1. Introduction

Airway remodeling refers to structural and functional changes in bronchial walls caused by inflammation and repeated cycles of injury and repair <sup>[1]</sup>. In asthma, it is characterized by structural and functional alterations of airway epithelium and subepithelial fibrosis, with thickening of the basement membrane and increased deposition of extracellular matrix (ECM) proteins in submucosa being the most prominent features <sup>[2]</sup>. Thickening of the basement membrane occurs mainly in the lamina reticularis layer named reticular basement membrane (RBM), which is composed of collagen fibers (mostly type III) produced primarily by underlying connective tissue cells <sup>[2][3]</sup>. There are more than twenty different subtypes of collagen, of which collagens I and III constitute the structural framework of lungs. In the asthmatic airways, collagen deposits accumulate in the basement membrane in a disorganized and fragmented form <sup>[4]</sup>. In contrast, type IV collagen is present mainly in the basal lamina, where it forms the central platform for anchoring epithelial cells <sup>[5]</sup>.

Increased smooth muscle mass and increased airway wall stiffness is another consistent trait of airway remodeling that correlates with impaired lung function in asthma <sup>[6][7]</sup>. However, it may also protect against exaggerated responses to allergens and other inflammatory stimuli, preventing immediate bronchoconstriction <sup>[8]</sup>. Progression of remodeling has been linked with chronic airway inflammation, although the causal relationship is uncertain <sup>[9]</sup>. Nevertheless, repeated mechanical stress may cause bronchial wall structural changes even in the absence of inflammation <sup>[10]</sup>.

Various features of airway remodeling, such as loss of epithelial cells and mucus cell hyperplasia, RBM thickening, and smooth muscle hypertrophy, can be described using a histological examination of airway mucosa <sup>[11]</sup>. However, emerging non-invasive methods, including lung computed tomography (CT) imaging, provide important remodeling measures that might be useful in quantifying bronchial wall thickening in a standardized and more comprehensive way <sup>[12][13]</sup>.

Integrins are a large family of transmembrane glycoproteins that mediate cell-cell and cell-ECM interactions, and thus are involved in a broad range of cellular processes, including cell adhesion, migration, and proliferation <sup>[14]</sup>. Each integrin subfamily is characterized by a common  $\beta$  subunit and non-

covalently associated variable  $\alpha$  chain. The  $\beta_1$ -subfamily includes, among others, integrins  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_{10}\beta_1$ , and  $\alpha_{11}\beta_1$  that are characterized by high-affinity binding to GFOGER-like motifs in collagen. Integrins  $\alpha_1\beta_1$  and  $\alpha_2\beta_1$ , which show a preference for binding to type IV and I collages, respectively, are essential members within that subset [14]. They are expressed on various cells, including vascular and epithelial cells, fibroblasts, and activated T-cells, responsible for the cell interactions with collagen fibers in basement membranes and ECM [15][16]. Therefore, both may be involved in asthma airway remodeling pathology. In an early report, Schuliga et al. [17] showed that interaction of airway smooth muscle cells with type I collagen via  $\alpha_2\beta_1$  integrin potentiated conversion of plasminogen into plasmin with subsequent degradation of ECM proteins. Furthermore, it has been demonstrated that in vitro inhibition of  $\alpha_2\beta_1$  integrin on fibroblasts enhanced their proliferation together with excessive lung ECM deposition and tissue fibrosis [18], supporting the concept of the potential antifibrotic role of  $\alpha_2\beta_1$  integrin in airways.

A growing body of evidence suggests that T-cell interactions with ECM proteins in perivascular tissues are essential for regulating the inflammatory response [19]. Furthermore, collagen-binding integrins not involved in cell migration occurred to be crucial costimulatory molecules of effector T cells [19][20]. Moreover, it has been demonstrated that  $\alpha_2\beta_1$  integrin may promote the survival of effector T cells by inhibiting Fas-induced apoptosis [21]. Although naïve T cells express very low levels of  $\alpha_1\beta_1$  and  $\alpha_2\beta_1$  integrins, they become abundant upon in vitro activation [19]. Asthma is an airway disease with a locally limited inflammatory response. However, increased blood levels of inflammatory cytokines and signs of coagulation pathway activation suggest accompanying low-grade systemic inflammation [22][23]. Thus, activated immune and effector cells, such as T-cells and eosinophils, although essential for airway site, may also be found in the systemic circulation likely primed in airways or by circulating inflammatory cytokines.

## 2. Clinical Characteristics and Airway Inflammatory Signature in Asthma Patients with Persistent Airflow Limitation

We analyzed 92 adult, non-smoking asthma patients and 36 controls. Among asthmatics, 47 subjects were characterized by persistent airflow limitation, while 45 had normal spirometry before or after a bronchodilator (non-persistent airflow limitation subtype). All three analyzed groups were similar in demographic variables, including body mass index (BMI), and past smoking, although asthma patients with persistent airflow limitation were older than the remaining asthmatics (Table 1). The studied asthma subtypes did not differ in disease duration and severity, staged according to the Global Initiative for Asthma (GINA) guidelines [24]. Atopy was more frequent in asthmatics. Other comorbidities were equally prevalent in all three analyzed groups, except for gastroesophageal reflux disease (GERD), which was more prevalent in the control individuals (Table 1).

**Table 1.** Demographic and clinical characteristics of the subjects studied.

Non-Persistent Airflow Limitation n = 45	Persistent Airflow Limitation n = 47	Control n = 36	p-Value Non-Persistent vs. Persistent Limitation	p-Value Non- Persistent Limitation vs. Control	p-Value Persistent Limitation vs. Control	
<b>Demographic variables</b>						
Age, years	52 (41-59)	58 (52-65)	55 (45-65)	<b>0.004</b>	0.07	0.27
Male gender, n (%)	10 (22)	16 (34)	5 (14)	0.15	0.5	0.07
Body mass index, kg/m <sup>2</sup>	27.8 (24.8-30.8)	26.4 (23.5-31.6)	27.3 (23.0-27.9)	0.53	0.13	0.95
<b>Smoking history</b>						

<b>Non-Persistent Airflow Limitation n = 45</b>	<b>Persistent Airflow Limitation n = 47</b>	<b>Control n = 36</b>	<b>p-Value Non-Persistent vs. Persistent Limitation</b>	<b>p-Value Non- Persistent Limitation vs. Control</b>	<b>p-Value Persistent Limitation vs. Control</b>	
Past smoking, n (%)	13 (29)	15 (32)	12 (33)	0.93	0.85	0.92
Pack-years of smoking	0 (0-7)	0 (0-8)	0 (0-4)	0.85	0.84	0.9
<b>Comorbidities</b>						
Atopy, n (%)	27 (60)	23 (49)	6 (17)	0.39	<b>0.0002</b>	<b>0.005</b>
GERD, n (%)	16 (36)	22 (47)	23 (64)	0.38	<b>0.02</b>	0.19
Arterial hypertension, n (%)	18 (40)	28 (60)	15 (42)	0.09	0.94	0.16
Diabetes mellitus, n (%)	6 (13)	12 (26)	3 (8)	0.23	0.72	0.08
Hypercholesterolemia, n (%)	9 (20)	16 (34)	6 (17)	0.2	0.92	0.13
Coronary heart disease, n (%)	2 (4)	5 (11)	2 (6)	0.47	0.77	0.67
<b>Asthma-related variables</b>						
Asthma duration, years	11.5 (5-19.5)	10 (7-20)		0.86		
Asthma severity (GINA): persistent mild, n (%)	8 (18)	7 (15)				
persistent moderate, n (%)	22 (49)	15 (32)				
persistent severe, n (%)	15 (33)	25 (53)		0.14		
Asthma treatment: Inhaled corticosteroids, n (%)	45 (100)	47 (100)				
Long-acting $\beta$ 2-agonists, n (%)	31 (69)	42 (89)				
Montelukast, n (%)	9 (20)	4 (9)				
Theophylline, n (%)	4 (9)	10 (21)				
Oral corticosteroids, n (%)	8 (18)	15 (32)		0.17		
<b>Spirometry results</b>						
FEV <sub>1</sub> before bronchodilator, L	2.79 $\pm$ 0.76	1.79 $\pm$ 0.8	2.71 $\pm$ 0.75	<b>&lt;0.001</b>	0.65	<b>&lt;0.001</b>
FEV <sub>1</sub> before bronchodilator, % of the predicted value	100.3 (89.5-111.1)	66.7 (54.1-80.6)	110.9 (106.8-114.7)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
FEV <sub>1</sub> after bronchodilator, L	2.92 $\pm$ 0.73	2.07 $\pm$ 0.95	2.84 $\pm$ 0.79	<b>&lt;0.001</b>	0.66	<b>&lt;0.001</b>
FEV <sub>1</sub> after bronchodilator, % of the predicted value	103.8 (96.4-116.5)	79.2 (62.8-87.2)	116 (112.1-122.3)	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
FEV <sub>1</sub> /VC (before bronchodilator)	73.3 (67.8-78.18)	59.1 (51.7-63.8)	74.84 (73.23-78.38)	<b>&lt;0.001</b>	0.16	<b>&lt;0.001</b>

Non-Persistent Airflow Limitation n = 45	Persistent Airflow Limitation n = 47	Control n = 36	p-Value Non-Persistent vs. Persistent Limitation	p-Value Non- Persistent Limitation vs. Control	p-Value Persistent Limitation vs. Control	
FEV <sub>1</sub> /VC (after bronchodilator)	76.99 (73.05– 81.88)	65.4 (54.5– 68.6)	79.33 (77.25– 80.38)	<b>&lt;0.001</b>	0.25	<b>&lt;0.001</b>

Table 1 footnote. Categorical variables are presented as numbers (percentages), continuous variables as median and interquartile range, or mean and standard deviation, as appropriate. Abbreviations: GERD—Gastroesophageal reflux disease, GINA—Global Initiative for Asthma, FEV<sub>1</sub>—Forced expiratory volume in 1 s, VC—Vital capacity, L-liter, n—number. Statistics: Mann-Whitney U-test or unpaired t-test, as appropriate.

Asthma patients showed higher serum IgE and increased red blood cell, lymphocyte, and monocyte counts compared to controls (Table 2). In turn, white blood cells and neutrophils were elevated in asthma patients with persistent airflow limitation than in other groups. Furthermore, asthma patients with persistent airflow limitation were characterized by elevated type-2 (T2) inflammatory biomarkers, such as blood and BAL eosinophilia, and serum periostin when comparing the remaining asthmatics (Table 2). Serum levels of a disintegrin and metalloproteinase domain-containing protein (ADAM)-33 were also increased in the asthma subtype with persistent airflow limitation (Table 2).

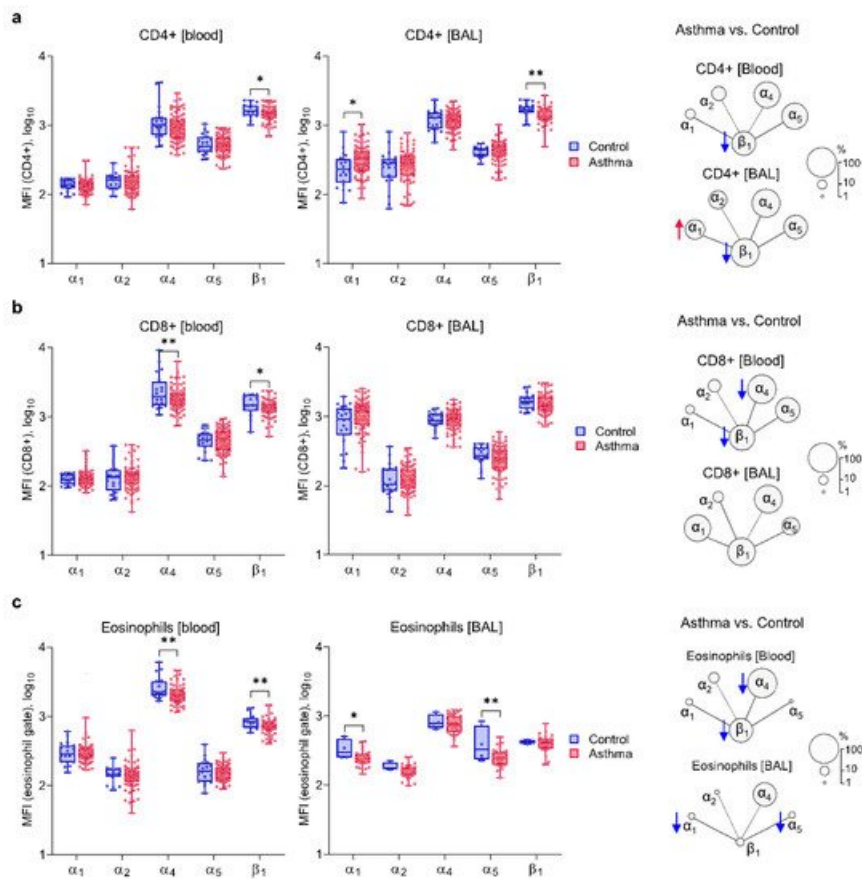
**Table 2.** Laboratory variables.

Reference Range	Non-Persistent Airflow Limitation n = 45	Persistent Airflow Limitation n = 47	Control n = 36	p-Value Non- Persistent vs. Persistent Limitation	p-Value Non- Persistent Limitation vs. Control	p-Value Persistent Limitation vs. Control
<b>Basic laboratory tests</b>						
Red blood cells, 10 <sup>6</sup> /μL	4-5	4.65 ± 0.4	4.7 ± 0.5	4.48 ± 0.4	0.68	<b>0.048</b> <b>0.03</b>
White blood cells, 10 <sup>3</sup> /μL	4-10	6.26 (5.43– 7.33)	7.44 (6.39– 9.25)	5.44 (5.16– 7.08)	<b>&lt;0.001</b>	0.07 <b>&lt;0.001</b>
Neutrophils, 10 <sup>3</sup> /μL	1.8-7.7	3.1 (2.7– 4.1)	3.7 (2.9– 4.8)	3.3 (2.9–3.6)	<b>0.049</b>	0.76 <b>0.04</b>
Lymphocytes, 10 <sup>3</sup> /μL	1-4.5	1.94 (1.58– 2.43)	2.2 (1.58– 2.61)	1.65 (1.44– 2.08)	0.5	<b>0.03</b> <b>0.03</b>
Monocytes, 10 <sup>3</sup> /μL	0.1-0.8	0.57 (0.49– 0.74)	0.71 (0.53– 0.9)	0.49 (0.41– 0.62)	<b>0.02</b>	<b>0.006</b> <b>&lt;0.001</b>
Blood platelets, 10 <sup>3</sup> /μL	140-400	223 (193– 247)	225 (191– 265)	228 (189–246)	0.78	0.98 0.85
<b>Asthma and inflammatory biomarkers (blood)</b>						
Eosinophilia/μL	40-450	230 (130– 310)	400 (180– 680)	110 (70-170)	<b>0.009</b>	<b>&lt;0.001</b> <b>&lt;0.001</b>

Reference Range	Non-Persistent Airflow Limitation n = 45	Persistent Airflow Limitation n = 47	Control n = 36	p-Value Non-Persistent vs. Persistent Limitation	p-Value Non-Persistent Limitation vs. Control	p-Value Persistent Limitation vs. Control	
Immunoglobulin E, IU/mL	0-100	90 (26-400)	88 (43-511)	23 (18-48)	0.6	<0.001	<0.001
C-reactive protein, mg/L	0-5	1.64 (0.53-8)	4.53 (0.58-9.38)	1.78 (0.89-2.29)	0.39	0.28	0.008
Fibrinogen, g/L	1.8-3.5	3.1 (2.8-3.5)	3.5 (3.2-4.2)	2.9 (2.3-3.7)	0.03	0.11	0.002
Periostin, ng/mL	0.29-0.61 §	0.28 (0.24-0.33)	0.38 (0.31-0.51)	0.37 (0.36-0.45)	0.01	0.001	0.85
Interleukin 6, pg/mL	0.005-1.432 §	0.72 (0.43-1.19)	1.09 (0.47-2.38)	0.57 (0.43-0.97)	0.14	0.29	0.03
Interleukin 10, pg/mL	0.163-1.022 §	0.6 (0.22-1.06)	0.55 (0.35-0.89)	0.43 (0.2-0.76)	0.95	0.17	0.1
Interleukin 12 (p70), pg/mL	0.005-2.618 §	0.005 (0.005-1.2)	0.005 (0.005-1.25)	0.005 (0.005-0.33)	0.7	0.13	0.26
ADAM-33, ng/mL	0.083-2.257 §	0.73 (0.2-1.29)	1.32 (0.33-2.37)	0.41 (0.13-1.5)	0.01	0.65	0.007
<b>Circulating integrin subunits</b>							
$\alpha_1$ integrin, ng/mL	6.45-103.67 §	17.32 (6.88-52.4)	32.7 (14.7-55.7)	24.1 (8.90-76.5)	0.14	0.21	0.83
$\alpha_2$ integrin, ng/mL	7.79-36.19 §	15.5 (9.7-25.5)	22.9 (15-39)	20.5 (11.7-26.5)	0.03	0.25	0.21
<b>Asthma and inflammatory biomarkers (bronchoalveolar lavage fluid)</b>							
Periostin, ng/mL	0.1-1.15 §	0.86 (0.8-0.99)	0.81 (0.72-0.95)	0.8 (0.51-0.88)	0.34	0.17	0.49
Eosinophils, %	0-1 #	0.5 (0-1)	1 (0.1-3)	0.1 (0-1)	0.02	0.62	0.006

### 3. Asthma Is Characterized by Decreased Expression of $\alpha_4$ and $\beta_1$ on Circulating Inflammatory Cells and Increased Expression of $\alpha_1$ Integrin Chain

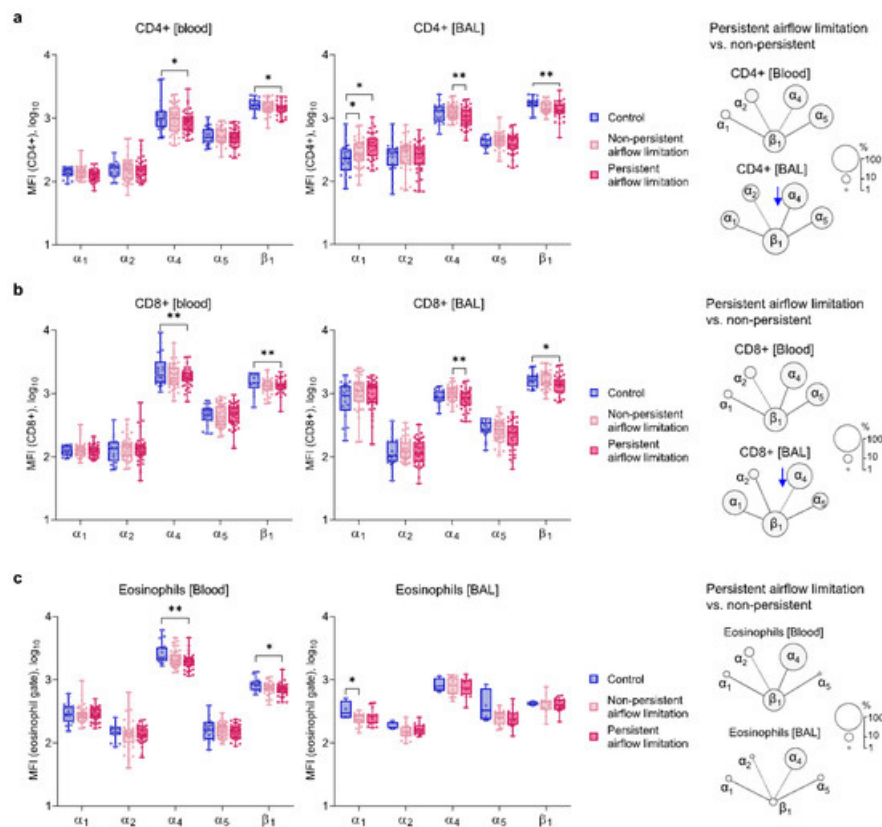
First, we analyzed the expression of  $\beta_1$ -subfamily integrins on blood and BAL inflammatory cells in asthma and control individuals. Surprisingly, blood CD8<sup>+</sup> T-cells and eosinophils in asthma were characterized by lower expression of  $\alpha_4$  and  $\beta_1$  integrin chains (Figure 1). Furthermore, circulating and airway CD4<sup>+</sup> T-cells showed lower expression of  $\beta_1$  integrin chains, whereas BAL CD4<sup>+</sup> T-cells additionally had increased expression of  $\alpha_1$  (Figure 1a). The  $\alpha_1$  integrin chain was also present on a higher percentage of blood eosinophils and blood CD8<sup>+</sup> T-cells.



**Figure 1.** Surface expression of integrin chains on T-cells and eosinophils in asthma and control subjects. Median fluorescent intensities (MFI) of the studied integrin chains in different compartments (on the left) and diagram summarizing the differences in the expression between the two analyzed groups (on the right, circle areas reflect the percentage of cells positive for a given integrin). **(a,b)** Asthma patients showed higher expression of  $\alpha_1$  integrin chain on bronchoalveolar lavage (BAL) CD4<sup>+</sup> T-cells (red arrow) and decreased expression of  $\beta_1$  (blue arrow) on CD4<sup>+</sup> blood and BAL and CD8<sup>+</sup> blood T-cells and lower expression of  $\alpha_4$  on blood CD4<sup>+</sup> T cells. **(c)** Lower expression of surface  $\alpha_4$  and  $\beta_1$  integrin chains on blood eosinophils and  $\alpha_1$  and  $\alpha_5$  on BAL eosinophils in asthma. Data presented as medians and range (T-cells: blood n = 108, BAL n = 101; eosinophils: blood n = 103, BAL n = 35;  $\beta_1$  was measured in 78% of samples). Statistics: ANCOVA with adjustment for age, sex, and BMI: \* p < 0.05, \*\* p < 0.01.

#### 4. Similar Expressions of $\alpha_1$ and $\alpha_2$ Integrin Chains on Blood and BAL Inflammatory Cells of Both Asthma Subsets

Next, we compared the expression of studied integrin subunits in persistent vs. non-persistent airflow limitation patients and controls. In comparison to the control group, patients with persistent airflow limitation showed lower expression of  $\alpha_4$  and  $\beta_1$  on both blood T-cell subsets and eosinophils and decreased  $\beta_1$  on BAL T-cells. Additionally, they were characterized by increased expression of  $\alpha_1$  integrin chain on BAL CD4<sup>+</sup> T cells, albeit once again only compared to the controls (Figure 2). They also had lower  $\alpha_4$  on BAL T-cells than those with non-persistent airflow limitation (Figure 2a,b). Compared to controls, the latter group had elevated  $\alpha_1$  on BAL CD4<sup>+</sup> T cells (Figure 2a).



**Figure 2.** Surface expression (median fluorescence intensity [MFI]) of integrin chains on T-cells and eosinophils in asthma patients with persistent vs. non-persistent airflow limitation and controls. **(a,b)** Patients with persistent airflow limitation showed lower expression of  $\alpha_4$  and  $\beta_1$  on both blood T-cell subsets, decreased  $\beta_1$  on both BAL T-cell subsets, and increased  $\alpha_1$  on BAL CD4<sup>+</sup> T-cells but only compared to controls. They also had lower  $\alpha_4$  on both BAL T-cell subsets comparing the non-persistent airflow limitation group (blue arrows in the diagram on the right). **(c)** Blood eosinophils of persistent airflow limitation patients had lower  $\alpha_4$  and  $\beta_1$  than controls and no difference compared to the non-persistent airflow limitation subgroup. Data are presented as medians and range (T-cells: blood n = 108, BAL n = 101; eosinophils: blood n = 103, BAL n = 35;  $\beta_1$  was measured in 78% of samples). Statistics: ANCOVA with adjustment for age, sex, and BMI: \* p < 0.05, \*\* p < 0.01.

Blood eosinophils in patients with persistent airflow limitation also had a lower expression of  $\alpha_4$  and  $\beta_1$  than in controls; they also did not differ from the non-persistent airflow limitation subgroup (Figure 2c).

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## Keywords

asthma;airway remodeling;computed tomography;biomarkers;histology