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Research Article
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Type 2 inflammation accelerates CD4$^+$ T-cell senescence in asthma

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Abstract: Asthma is a complex and chronic inflammatory airway disease associated with the abnormal activation of immune cells. T-cell senescence is linked to immune dysfunction and persistent inflammation, but the relationship between asthma and T-cell senescence remains unexplored. This study reveals significantly higher percentages of cluster of differentiation 4-positive (CD4$^+$) senescent T cells (Tsens) in asthma patients than in healthy controls, while CD8$^+$ Tsen percentages do not appear to increase. CD4$^+$ Tsen percentages in both the blood and sputum are positively correlated with fractional exhaled nitric oxide (FeNO) values, eosinophil abundance, and T helper type 2 (Th2) cell abundance in the blood. The clinical manifestations of asthma were recreated in a house dust mite (HDM)-induced mouse model. In HDM-exposed mice, CD4$^+$ Tsen percentages were also elevated in the lungs. To counteract T-cell senescence, therapeutic interventions, including interleukin-4 (IL-4) antibodies and dexamethasone, were administered to the mice. IL-4 neutralization reduced CD4$^+$ Tsen percentages and inhibited p38 mitogen-activated protein kinase (MAPK) activation. Adoptive transfer of CD4$^+$ Tsens did not induce spontaneous asthma in phosphate-buffered saline (PBS)-treated mice but exacerbated type 2 inflammation in HDM-treated mice. Our study revealed a significant increase in CD4$^+$ Tsen (CD57$^+$CD28$^-$) abundance in asthma patients and suggested that type 2 inflammation drives CD4$^+$ T-cell senescence in asthma. Furthermore, adoptive transfer of CD4$^+$ Tsens appears to exacerbate type 2 inflammation.

Key words: Asthma; Cellular senescence; T cells; Inflammation

1 Introduction

Asthma, a chronic inflammatory disease, is characterized by airway hyperresponsiveness and reversible airway obstruction (Huang et al., 2019). The Global Burden of Disease study identified asthma as one of the most prevalent chronic respiratory diseases globally (GBD Chronic Respiratory Disease Collaborators, 2020). Type 2 asthma is the most common phenotype and is typically associated with allergen sensitivity and T helper type 2 (Th2) cell-mediated immunity involving immunoglobulin E (IgE) (Ödling et al., 2018; Hammad and Lambrecht, 2021). Cell senescence, a state triggered by stress-induced damage and some physiological processes, is characterized by prolonged, often irreversible, cell-cycle arrest (Gorgoulis et al., 2019). Senescent human T cells lose the expression of costimulatory molecules, such as cluster of differentiation 27 (CD27) and CD28, while the expression of terminal differentiation markers, such as CD57, is upregulated (Mittelbrunn and Kroemer, 2021). Compared with nonsenescent cells, senescent cells display distinct characteristics, including increased activity of senescence-associated β-galactosidase (SA-β-Gal) (Childs et al., 2017), a higher percentage of killer-cell lectin-like receptor G1 (KLRG1) (Akbar et al., 2016), and elevated expression of programmed cell death protein 1 (PD-1) (Wang et al., 2022), as well as elevated levels of p16 (Wood et al., 2016) and p21 (Sturmlechner et al., 2021).

Cellular senescence is associated with chronic low-grade inflammation and is observed in several inflammatory diseases, including chronic obstructive pulmonary disease (COPD), renal disease, obesity-related metabolic syndrome, type I and type II diabetes, atherosclerosis, and Alzheimer's disease (Childs et al.,

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2015; López-Otín et al., 2023; Devulder, 2024). Systemic elevation of inflammatory mediator levels may contribute to early immunosenescence (Madruga et al., 2024). Previous studies have shown that airway smooth muscle cells in the lungs of elderly asthma patients exhibit increased expression of senescence markers, including p53, p21, and several senescence-associated secretory phenotype (SASP) components (Aghali et al., 2022). Additionally, increased cellular senescence has been observed in bronchial fibroblasts and myofibroblasts in the lungs of asthma patients (Schafer et al., 2017). Some immune cells, including macrophages, T cells, and B cells, may undergo senescence due to chronic inflammation and oxidative stress (Wang et al., 2020; Wan et al., 2023). Several factors, such as acute and chronic infection, cellular attrition, insufficient replacement of naive cells, and proliferative stress on naive T cells, make T cells particularly susceptible to senescence (Weyand et al., 2014). While the concept of T-cell senescence has been extensively studied in the context of viral infection and autoimmune disease, there are few studies on senescent T cells (Tsens) in asthma patients.

To investigate potential differences in T-cell senescence between asthma patients and healthy controls, we analyzed its occurrence in both human patients and a mouse model of asthma. Given the persistent inflammatory milieu in type 2 asthma, we hypothesized that type 2 inflammation may promote CD4$^+$ T-cell senescence and that CD4$^+$ Tsens could, in turn, influence airway inflammation. We combined analyses of patient samples with a house dust mite (HDM)-induced mouse model and complementary in vitro assays. Using type 2 pathway inhibition in vivo (anti-interleukin-4 (anti-IL-4) neutralization) and adoptive transfer approaches, we further examined potential drivers and functional implications of CD4$^+$ Tsens in the context of allergic airway inflammation.

2 Results

2.1 Clinical characteristics of asthma patients

The study included 50 asthma patients and 14 age-matched healthy controls, with some subjects providing induced sputum samples. The demographic and clinical characteristics of the participants are summarized in Tables 1 and S1. No significant differences in age, sex, body mass index (BMI), or smoking history were observed between the two groups. The flow cytometry results revealed that the percentage of Th2 cells in the blood of asthma patients was significantly greater than that in the blood of the control group, whereas the proportion of Th1 cells was lower (Table S2 and Fig. S1). Additionally, the proportions of Th17 and regulatory T (Treg) cells were elevated in the blood of asthma patients, but the Th17/Treg ratio was greater than that in the blood of healthy controls, suggesting that a Th17/Treg imbalance occurs in the peripheral blood of asthma patients. However, there were very few CD4$^+$ T cells in the sputum, and we observed no significant differences in Th2 cells or other conventional CD4$^+$ Th subsets between patients and controls (Table S3). The proportions of all Th subgroups were analyzed by gating for CD4$^+$ T cells.

2.2 Increased CD4$^+$ Tsen percentages in asthma patients

To mitigate the potential confounding effects of clinical characteristics, such as age and BMI, on Tsens, we matched these variables between asthma patients and healthy controls. Compared with the CD57$^-$CD28$^+$ (nonsenescent T cell (Tn)) subset, the CD57$^+$CD28$^-$ Tsen subset of CD4$^+$ or CD8$^+$ T cells presented greater SA-β-Gal activity (Fig. S2a). Moreover, the expression of p16 (Fig. S2b) and p21 (Fig. S2c) and the percentages of cells expressing KLRG1 (Fig. S2d), a marker of terminal differentiation, were significantly increased in Tsens in both asthma patients and controls. Among CD4$^+$ T cells, the percentage of PD-1-positive cells (Fig. S2e) was also significantly increased in Tsens, but this pattern was not observed in CD8$^+$ T cells. Notably, senescent CD57$^+$CD28$^-$ cells in both the CD4$^+$ and CD8$^+$ T-cell subsets consistently produced higher levels of IL-6 and interferon-γ (IFN-γ) than their nonsenescent counterparts (Figs. S2f and S2g). In summary, the CD57$^+$CD28$^-$ T-cell subset from asthma patients exhibited common features of senescent cells, which may provide markers for detecting Tsens in asthma.

In the peripheral blood, we found no significant difference in the proportion of CD4$^+$ or CD8$^+$ T cells between the two groups (Fig. 1a). Flow cytometry revealed that both the CD4$^+$ and CD8$^+$ T-cell populations contained senescent cells. Furthermore, the proportion of CD4$^+$ Tsens was significantly greater in asthma

Table 1 Demographics, characteristics, and clinical features of the subjects (blood donors)

Characteristics	Healthy control (n=14)	Asthma (n=50)	P-value
Age (years)	48.14±12.30	40.26±16.61	0.104
Sex, male	6 (42.8%)	22 (44.0%)	0.939
BMI (kg/m^2)	24.12±2.96	24.18±3.61	0.960
BMI categories			0.693
BMI<18.5 kg/m^2	0 (0.0%)	3 (6.0%)	
18.5 kg/m^2⩽BMI<24.0 kg/m^2	9 (64.3%)	27 (54.0%)	
24.0 kg/m^2⩽BMI<28.0 kg/m^2	4 (28.6%)	18 (36.0%)	
BMI⩾28.0 kg/m^2	1 (7.1%)	2 (4.0%)	
Smoking history, yes	2 (14.3%)	5 (10.0%)	0.648
Acute asthma exacerbation history, yes		6 (12.0%)	
Age of onset (years)		37.69±14.69	
FEV1/pred (%)	97.19±17.27	85.87±15.42	0.038
FEV1/FVC (%)	85.82±3.30	78.15±6.90	0.001
ACT		19.03±4.17	
FeNO (ppb)		74.30±53.57	
IgE		140.0 (509.8)	
Eosinophils (×10^9 L^{-1})	0.15±0.16	0.37±0.25	0.003
Total sputum cells (×10^6 mL^{-1})		0.88±0.75	
Sputum macrophages (%)		14.13±20.04	
Sputum lymphocytes (%)		6.10±5.73	
Sputum neutrophils (%)		65.23±30.83	
Sputum eosinophils (%)		14.52±22.98	

BMI: body mass index; FEV1: forced expiratory volume in 1 s; Pred: predicted; FVC: forced vital capacity; ACT: asthma control test; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E. 1 ppb=1×10^{-9}. Continuous variables are presented as mean±standard deviation (SD), categorical variables are shown as number (percentage), and non-normally distributed variables are summarized as median (interquartile range). P-values were derived using t-tests for continuous data and χ^2-tests for categorical data.

patients ((2.43±1.37)%) than in healthy controls ((1.43±0.65)%) (P<0.05; Fig. 1a). However, no significant difference in the proportion of CD8$^+$ Tsens was detected between asthma patients ((23.48±6.42)%) and healthy controls ((21.18±4.16)%) (P>0.05). We did not observe any differences in CD4$^+$CD57$^-$CD28$^+$ or CD8$^+$CD57$^-$CD28$^+$ Tn cells between the two groups (Fig. 1a). The proportion of CD4$^+$ Tsens in the sputum of asthma patients was greater than that in the sputum of healthy controls (Fig. 1d), indicating that asthma patients had more CD4$^+$ Tsens in both the peripheral blood and the local airway. CD4$^+$ Tsens also showed potential as a distinguishing feature between individuals with and without asthma, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.716 (P<0.05; Fig. 1b).

2.3 Differences in CD4$^+$ Tsen abundance between different clinical phenotypes of asthma

To explore the relationships between CD4$^+$ Tsen abundance and different asthma phenotypes, we stratified patients according to various classification criteria (Figs. 1f–1l). CD4$^+$ Tsen percentages were significantly elevated in patients with poorly controlled asthma (asthma control test (ACT) score <20) compared with patients with well controlled asthma (ACT score ⩾20) (Fig. 1j). We also assessed various senescence-related proinflammatory cytokines in the peripheral blood (Table S4). The results revealed that the levels of IFN-γ, tumor necrosis factor-α (TNF-α), IL-1β, IL-6, IL-17A, IL-23, and IL-33 were significantly greater in asthma patients than in controls (Table S4, Fig. S3a).

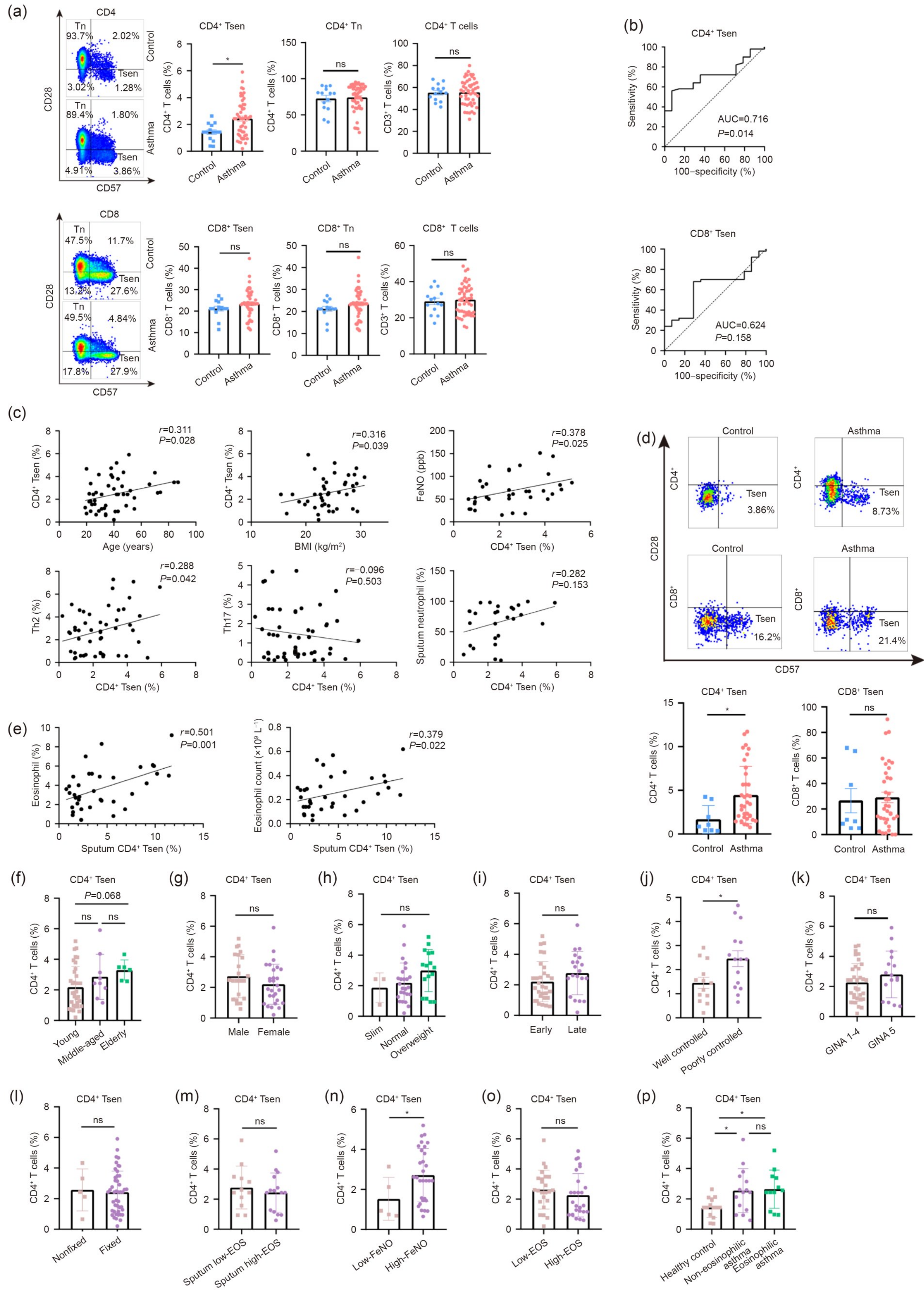

Fig. 1 Increased abundance of cluster of differentiation 4-positive ($CD4^+$) senescent T cells (Tsens) in patients with asthma. (a) Representative flow cytometry plots and statistical analysis of the percentages of total $CD4^+$ T cells, total $CD8^+$ T cells, the $CD28^+CD57^-$ nonsenescent T-cell (Tn) subset, and the $CD28^-CD57^+$ Tsen subset in the blood of patients with asthma (*n*=50) compared with healthy controls (*n*=14). (b) Receiver operating characteristic (ROC) curves of $CD4^+$ Tsen and $CD8^+$ Tsen percentages in patients with asthma (*n*=50) and healthy controls (*n*=14). (c) Correlations between the percentage of $CD4^+$ Tsens in the blood from patients with asthma (*n*=50) and age, body mass index (BMI), fractional exhaled nitric oxide (FeNO) values, percentages of Th2 and Th17 cells, and the sputum neutrophil percentage. (d) Representative flow cytometry plots and statistical analysis showing the percentages of the $CD28^-CD57^+$ (Tsen) subsets for $CD4^+$ and $CD8^+$ T cells in the sputum from patients with asthma (*n*=36) compared with those from healthy controls (*n*=8). (e) Correlations between the percentage of $CD4^+$ Tsens in the sputum from patients with asthma (*n*=36) and the cell counts and percentages of eosinophils in the blood. (f–p) Percentages of $CD4^+$ Tsens in patients with different ages (f, *n*=35/9/6), different genders (g, *n*=22/28), different body mass indexes (BMIs) (h, *n*=3/25/16), different ages of onset (i, *n*=30/20), well controlled (asthma control test (ACT) score of ⩾20, *n*=13) and poorly controlled (ACT score of <20, *n*=15) asthma (j), the Global Initiative for Asthma (GINA) 1–4 (*n*=34) and GINA 5 (*n*=16) treatment stages (k), nonfixed (*n*=5) and fixed (*n*=45) airflow limitation (l), sputum low-eosinophil (low-EOS) (sputum eosinophil ratio of <2%, *n*=12) and high-eosinophil (high-EOS) (sputum eosinophil ratio of ⩾2%, *n*=15) counts (m), FeNO<20 ppb (1 ppb=1×10^{-9}) and FeNO⩾20 ppb (n, *n*=5/29), hypoeosinophilia (eosinophil number of <150 cells/μL, *n*=24) and hypereosinophilia (eosinophil number of ⩾150 cells/μL, *n*=26) (o), and healthy controls, non-eosinophilic asthma (sputum eosinophil percentage of <3%), and eosinophilic asthma (sputum eosinophil percentage of ⩾3% and sputum neutrophil percentage of <61%) (p, *n*=14/16/12). Correlation analysis was performed using Spearman's rank correlation coefficient. The data from different groups were statistically analyzed using *t*-tests and analysis of variance (ANOVA). The bars show means with standard errors of the means. $^*P<0.05$; ns (not significant), *P*>0.05.

Furthermore, the levels of the senescence-related cytokines IL-6 and IL-17A were significantly negatively correlated with ACT scores (Fig. S3b), suggesting that poorer asthma control was associated with higher levels of SASP components such as IL-6 in the peripheral blood.

We also found that the percentage of $CD4^+$ Tsens was positively associated with age and BMI in asthma patients (Fig. 1c), and that elderly patients (⩾60 years old) presented higher percentage of $CD4^+$ Tsens than young patients did (18–44 years old) (*P*=0.068; Fig. 1f). However, no significant differences in $CD4^+$ Tsen abundance were found across subgroups delineated on the basis of sex or other factors (Figs. 1g–1i, 1k, and 1l).

2.4 Positive correlation between $CD4^+$ Tsen abundance and type 2 inflammation in asthma

Most asthma patients present with type 2 inflammation, characterized by the blood eosinophil number of ⩾150 cells/μL, FeNO value of ⩾20 ppb (1 ppb=1×10^{-9}), sputum eosinophil percentage of ⩾2%, and/or clinical allergen-driven asthma. We investigated the association between $CD4^+$ Tsen abundance and type 2 inflammation, and found that the FeNO value was significantly positively correlated with the proportion of $CD4^+$ Tsens (*r*=0.378, *P*=0.025; Fig. 1c) and that the percentage of Th2 cells in the blood was also significantly positively correlated with the proportion of $CD4^+$ Tsens (*r*=0.288, *P*=0.042; Fig. 1c). However, no significant correlation was detected between the proportion of neutrophils in the sputum or Th17 cells in the blood and the proportion of $CD4^+$ Tsens in the blood (Fig. 1c). Moreover, we found significant positive correlations between $CD4^+$ Tsen abundance in the sputum and both the proportion and number of eosinophils in the peripheral blood (Fig. 1e). Correlation analysis suggested that $CD4^+$ Tsen abundance was positively correlated with type 2 inflammation in asthma patients. Subgroup analysis according to asthma endotype (Figs. 1m–1p) further revealed that patients with FeNO⩾20 ppb had more $CD4^+$ Tsens ((2.71±1.33)%) than those with FeNO<20 ppb ((1.58±1.07)%) (*P*=0.0429; Fig. 1n), highlighting the importance of targeting type 2 inflammation in asthma treatment.

2.5 Significantly elevated $CD4^+$ Tsen percentages in mice with HDM-induced asthma

$CD4^+$ Tsen abundance was significantly positively correlated with type 2 inflammation, but it remained unclear whether the observed increase in senescent cell abundance was directly caused by type 2 inflammation. To address this question, we used an HDM-induced mouse model of asthma, which is dominated by type 2 inflammation (Fig. S4a). Compared with control mice, HDM-treated mice presented significantly increased resistance of the respiratory system (R_{rs}) following exposure to increasing concentrations of methacholine (Fig. 2a). Histological examination after hematoxylin and eosin (H&E) staining revealed more severe

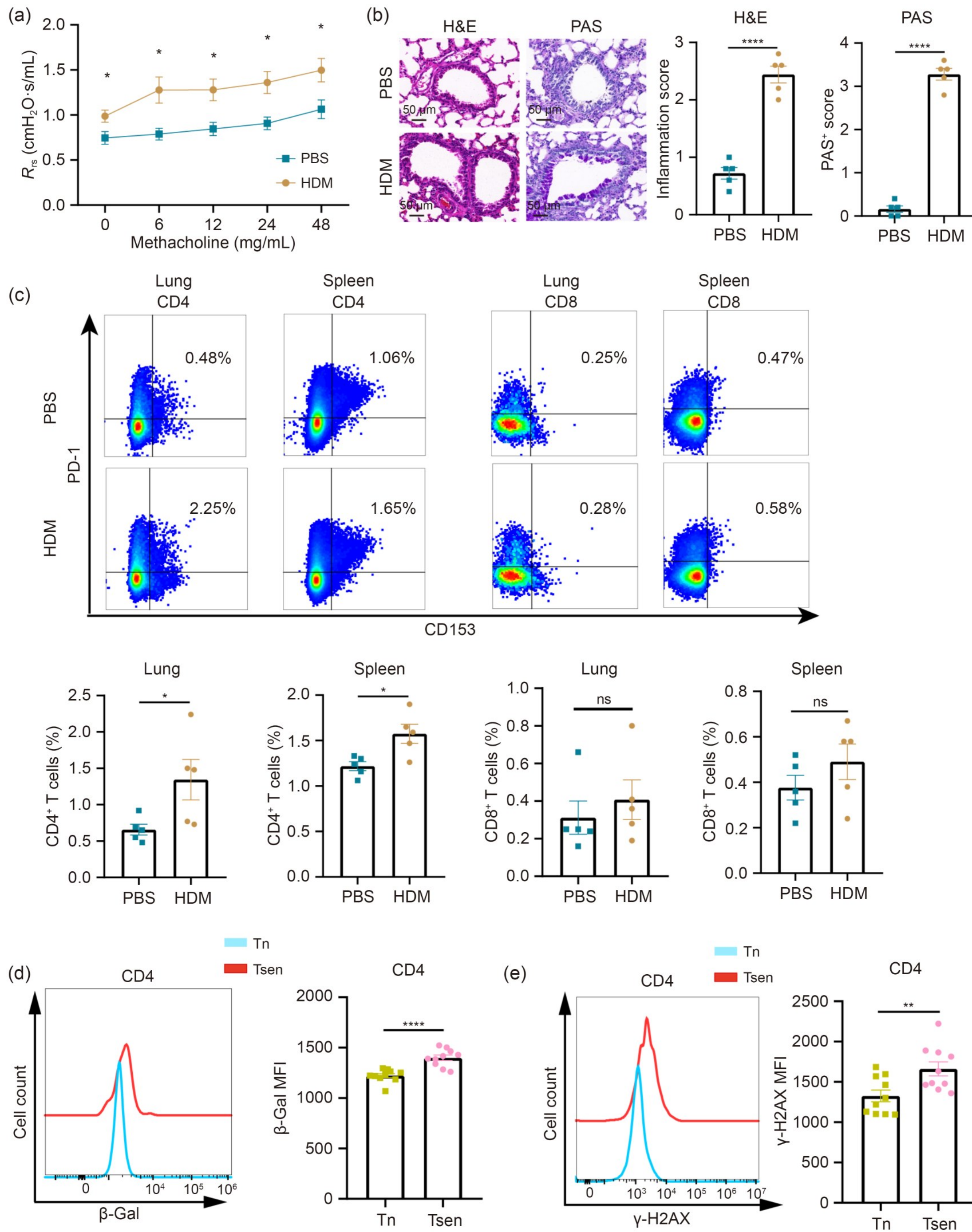

Fig. 2 Increased cluster of differentiation 4-positive (CD4$^+$) senescent T-cell (Tsen) abundance in mice with asthma. (a) Total resistance of the respiratory system (R_{rs}) in mice (n=5) treated with increasing concentrations of methacholine (0–48 mg/mL). 1 cmH$_2$O=98.0665 Pa. (b) Representative images and statistical analyses of hematoxylin and eosin (H&E)- and periodic acid-Schiff (PAS)-stained lung sections from each group (n=5). (c) Representative flow cytometry plots and statistical analysis of the percentages of the CD153$^-$PD-1$^-$ (nonsenescent T-cell (Tn)) and CD153$^+$PD-1$^+$ (Tsen) subsets among CD4$^+$ and CD8$^+$ T cells in the lungs and spleens of mice with asthma compared with those of controls (n=5). (d, e) Representative flow cytometry plots and statistical analysis of the mean fluorescence intensity (MFI) of senescence-associated β-galactosidase (SA-β-Gal) (d) and phosphorylated histone H2AX at Ser139 (γ-H2AX) (e) expression (n=10). The data from different groups were statistically analyzed via t-tests. The bars show the means with standard errors of the means. * P<0.05; ** P<0.01; **** P<0.0001; ns (not significant), P>0.05. PBS: phosphate-buffered saline; HDM: house dust mite.

bronchial and perivascular inflammatory cell infiltration in the asthma group than in the control group (Fig. 2b). Periodic acid-Schiff (PAS) staining further revealed significantly greater airway mucus hypersecretion in asthmatic mice (Fig. 2b). Since mouse T cells do not express the CD57 antigen, we used CD153 and PD-1 to characterize Tsens (Yoshida et al., 2020). CD153 (also known as tumor necrosis factor superfamily member 8 (TNFSF8) or CD30 ligand (CD30L)) is a membrane-binding protein that belongs to the tumor necrosis factor superfamily, is expressed on activated T cells, and is increasingly recognized as a marker of senescent cells (Yoshida et al., 2020). The percentages of $CD4^+$ Tsens in the lungs and spleens of asthmatic mice were significantly greater than those in the lungs and spleens of control mice; however, no significant difference in $CD8^+$ Tsen abundance was observed between the two groups (Fig. 2c). Compared with mouse $CD4^+$ Tn cells ($CD153^-PD\text{-}1^-$), $CD4^+$ Tsens ($CD153^+PD\text{-}1^+$) exhibited higher levels of SA-β-Gal and phosphorylated histone H2AX at Ser139 (γ-H2AX) (Figs. 2d and 2e). These findings suggest that the $CD4^+$ T-cell senescence phenotype observed in the mouse asthma model closely resembles that observed in humans.

2.6 Effects of anti-IL-4 antibody treatment on $CD4^+$ Tsen abundance in HDM-treated mice

To further explore the causal relationship between type 2 inflammation and $CD4^+$ T-cell senescence, we treated mice with HDM-induced asthma with monoclonal anti-IL-4 antibodies to neutralize IL-4, a key cytokine involved in type 2 inflammation, and dexamethasone, a nonspecific anti-inflammatory agent (Fig. S4b). Both treatments significantly reduced airway resistance (Fig. 3a) and decreased the proportion or number of eosinophils, as well as the percentages of Th2 cells, in the blood, bronchoalveolar lavage fluid (BALF), and lung tissue of asthmatic mice (Figs. 3b–3f). In addition, these treatments alleviated lung inflammation and mucus hypersecretion (Figs. 3g and 3h). It is notable that treatment with either the anti-IL-4 antibody or dexamethasone significantly reduced the proportion of $CD4^+$ Tsens in the lungs and spleens (Fig. 3i) and reduced SA-β-Gal activity in $CD4^+$ T cells in the lungs (Fig. 3j).

Recent studies have suggested that IL-4 activates multiple signal transduction pathways, such as the signal transducer and activator of transcription 6 (STAT6) and p38 mitogen-activated protein kinase (MAPK) pathways, which are considered potential mechanisms for inducing cellular senescence (Min et al., 2022). We analyzed the phosphorylation of proteins involved in these signaling pathways in the lung tissue of HDM-treated mice and found that the phosphorylation of STAT6 and p38 MAPK was significantly increased (Figs. 4a and 4b). However, in the mice treated with the anti-IL-4 antibody, the phosphorylated p38 MAPK (p-p38 MAPK) and total p38 MAPK were significantly reduced and phosphorylated STAT6 (p-STAT6) remained unchanged (Figs. 4a and 4b). To verify the effects of IL-4, IL-5, and IL-13 on $CD4^+$ T cells in vitro, we isolated human $CD4^+$ T cells and cultured them with various concentrations of IL-4, IL-5, and IL-13. SA-β-Gal staining revealed that IL-4, IL-13, and high concentrations of IL-5 significantly increased SA-β-Gal activity in $CD4^+$ T cells (Fig. 4c), suggesting that type 2 inflammatory cytokines can induce $CD4^+$ T-cell senescence. We investigated the mechanism of IL-4 in human peripheral-blood-derived $CD4^+$ T cells and found that IL-4 stimulation enhanced the phosphorylation of p38 MAPK without affecting STAT6 phosphorylation (Figs. 4d and 4e). Flow cytometry analysis revealed that the addition of the p38 MAPK inhibitor (SB202190) significantly reduced SA-β-Gal activity compared to IL-4 stimulation alone (Fig. 4f).

2.7 Promotion of type 2 inflammation by adoptive transfer of $CD4^+$ Tsens

To investigate the role of $CD4^+$ Tsens in the pathogenesis of asthma, we performed adoptive transfer of $CD4^+$ Tsens into healthy or asthmatic mice (Fig. S4c). Since it is difficult to acquire sufficient numbers of $CD4^+$ Tsens from patients or asthmatic mice for adoptive transfer, we isolated $CD4^+$ T cells from the spleens of these mice and induced senescence with doxorubicin (Dox). We found that 50 nmol/L Dox efficiently induced $CD4^+$ T-cell senescence, as evidenced by increased β-Gal activity, induction of the $CD153^+PD\text{-}1^+$ phenotype, and increased levels of p16 and γ-H2AX (Fig. 5a). These findings suggest that Dox-treated $CD4^+$ T cells exhibit phenotypic characteristics similar to those of $CD4^+$ Tsens. We then performed adoptive transfer of Dox-induced $CD4^+$ Tsens or control $CD4^+$ T cells into healthy mice. Mice that received $CD4^+$ Tsens exhibited increased proportions

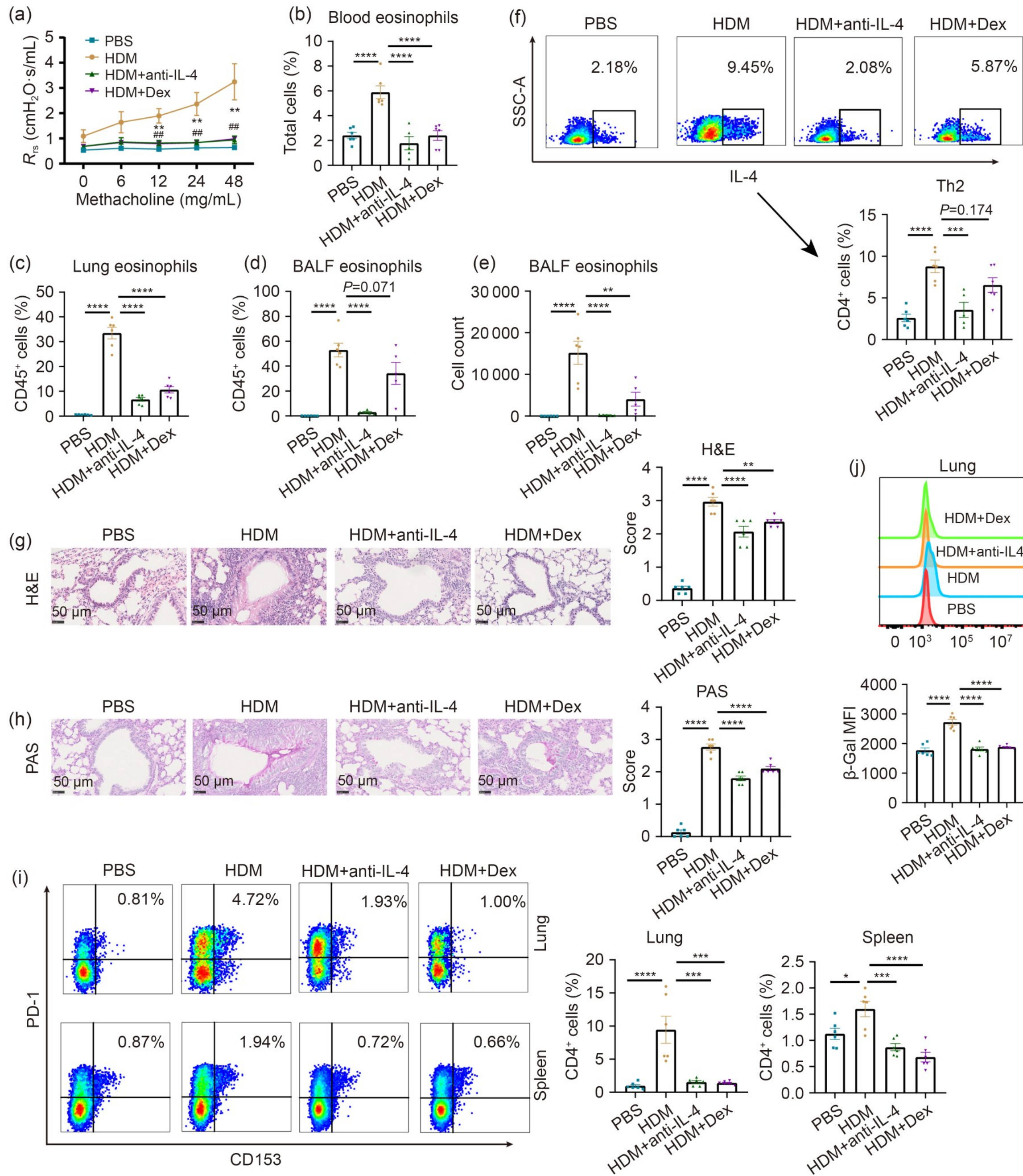

Fig. 3 Ability of interleukin-4 (IL-4) antibody and dexamethasone (Dex) injection to exert therapeutic effects by preventing cluster of differentiation 4-positive (CD4$^+$) senescent T-cell (Tsen) accumulation and type 2 inflammation in mice with asthma. (a) Total resistance of the respiratory system (R_{rs}) of mice (*n*=5/6) treated with increasing concentrations of methacholine (0–48 mg/mL). 1 cmH$_2$O=98.0665 Pa. ** *P*<0.01, HDM+anti-IL-4 vs. HDM; $^{##}$ *P*<0.01, HDM+Dex vs. HDM. (b–e) Statistical analysis of the percentages of eosinophils in the blood (b), lungs (c), and bronchoalveolar lavage fluid (BALF) (d) and the cell counts of eosinophils in mouse BALF (e) (*n*=5/6). (f) Representative flow cytometry plots and statistical analysis of the percentages of T helper type 2 (Th2) cells in mouse lungs (*n*=5/6). (g, h) Representative images and statistical analyses of hematoxylin and eosin (H&E)- and periodic acid-Schiff (PAS)-stained lung sections from each group (*n*=6). (i) Representative flow cytometry plots and statistical analysis of the percentages of CD153$^+$PD-1$^+$ CD4$^+$ Tsens in mouse lungs and spleens (*n*=6). (j) Representative flow cytometry plots and statistical analysis of the mean fluorescence intensity (MFI) of senescence-associated β-galactosidase (SA-β-Gal) activity in CD4$^+$ T cells in mouse lungs (*n*=6). The bars show the means with standard errors of the means. * *P*<0.05; ** *P*<0.01; *** *P*<0.001; **** *P*<0.0001. PBS: phosphate-buffered saline; HDM: house dust mite; SSC-A: side scatter-area; PD-1: programmed cell death protein 1.

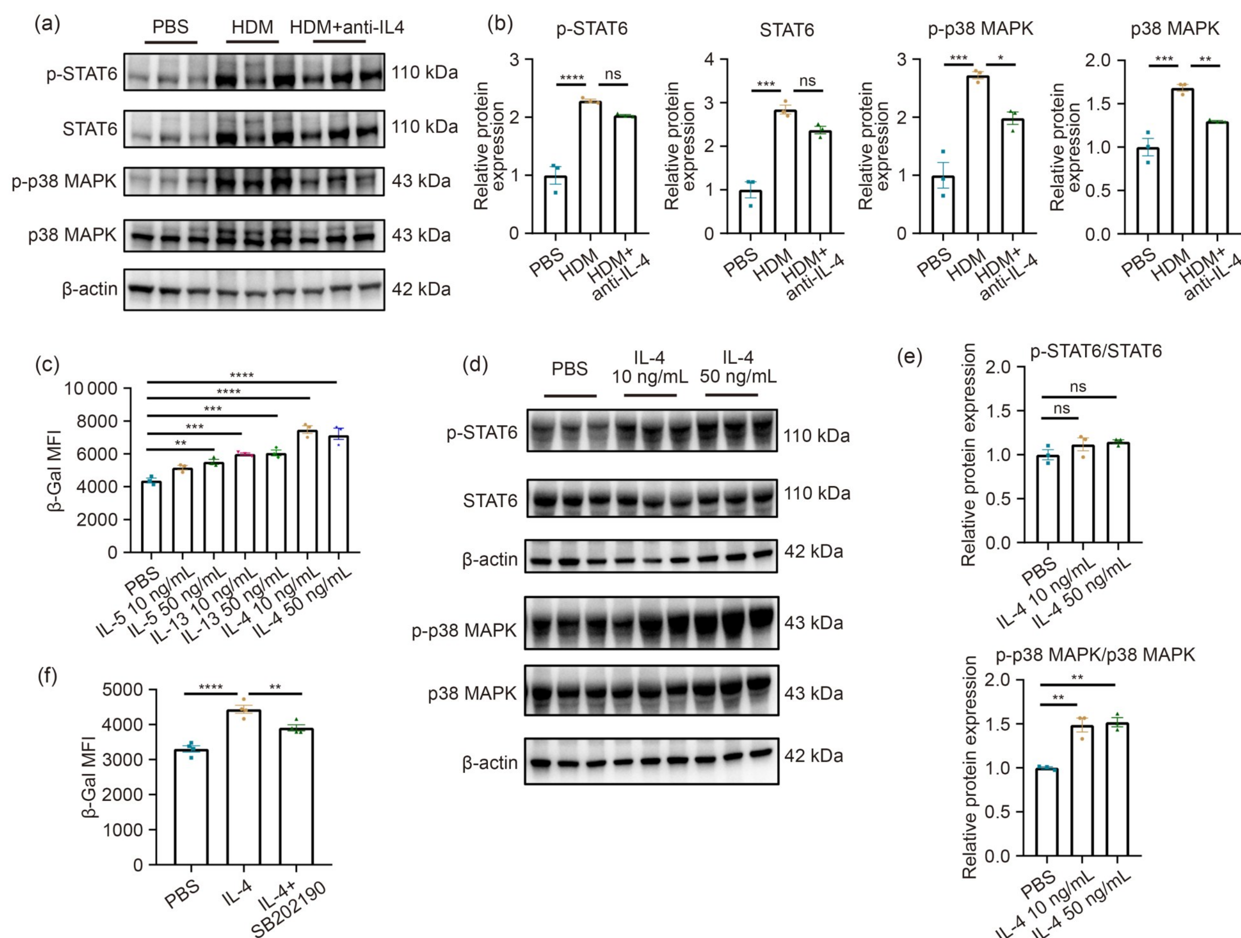

Fig. 4 Induction of cluster of differentiation 4-positive ($CD4^+$) T cell senescence by type 2 inflammatory cytokine interleukin-4 (IL-4). (a, b) Western blot and quantification of the phosphorylated (p-) and total protein levels of p38 mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 6 (STAT6) in the lungs of mice (*n*=3) treated with phosphate-buffered saline (PBS), house dust mite (HDM), and HDM+anti-IL-4 antibody. (c) Senescence-inducing effects of different concentrations of IL-4, IL-5, and IL-13 on human $CD4^+$ T cells (*n*=3). (d, e) Western blot and quantification of the phosphorylated (p-) and total protein levels of p38 MAPK and STAT6 in human $CD4^+$ T cells treated with PBS or IL-4 (*n*=3). (f) Statistical diagram of the mean fluorescence intensity (MFI) of senescence-associated β-galactosidase (SA-β-Gal) activity in human $CD4^+$ T cells treated with IL-4 or IL-4 combined with p38 MAPK inhibitor (SB202190) (*n*=4). The bars show the means with standard errors of the means. $^*P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$; $^{****}P<0.0001$; ns (not significant), $P>0.05$.

of $CD4^+$ Tsens in the lung and spleen, along with increased SA-β-Gal activity in $CD4^+$ T cells in the lung (Figs. 5b and 5c). However, these mice did not exhibit increased airway resistance (Fig. 5d) or an elevated proportion of eosinophils (Fig. 5f) or Th2 cells (Fig. 5g) in the lung, nor did they show significant mucus hypersecretion (Fig. 5i). Interestingly, there were significant increases in the abundance of eosinophils in the BALF (Fig. 5e) and in the infiltration of inflammatory cells into the lung (Fig. 5h). These results suggest that while adoptive transfer of $CD4^+$ Tsens does not induce spontaneous asthma in healthy mice, it does promote local inflammation in the lungs.

We also performed adoptive transfer of $CD4^+$ Tsens from HDM-treated mice (Fig. S4c). Mice that received these $CD4^+$ Tsens exhibited increased proportions of $CD4^+$ Tsens in the lungs, as well as increased SA-β-Gal activity in $CD4^+$ T cells in the lungs (Fig. 6a). These mice also showed significant increases in airway resistance (Fig. 6b), eosinophil abundance, and Th2-cell abundance in the lung and BALF (Figs. 6c–6f). Moreover, lung inflammation and mucus hypersecretion were significantly increased in these mice (Figs. 6g and 6h). These findings suggest that $CD4^+$ Tsens exacerbate type 2 inflammation in asthma through positive feedback mechanisms.

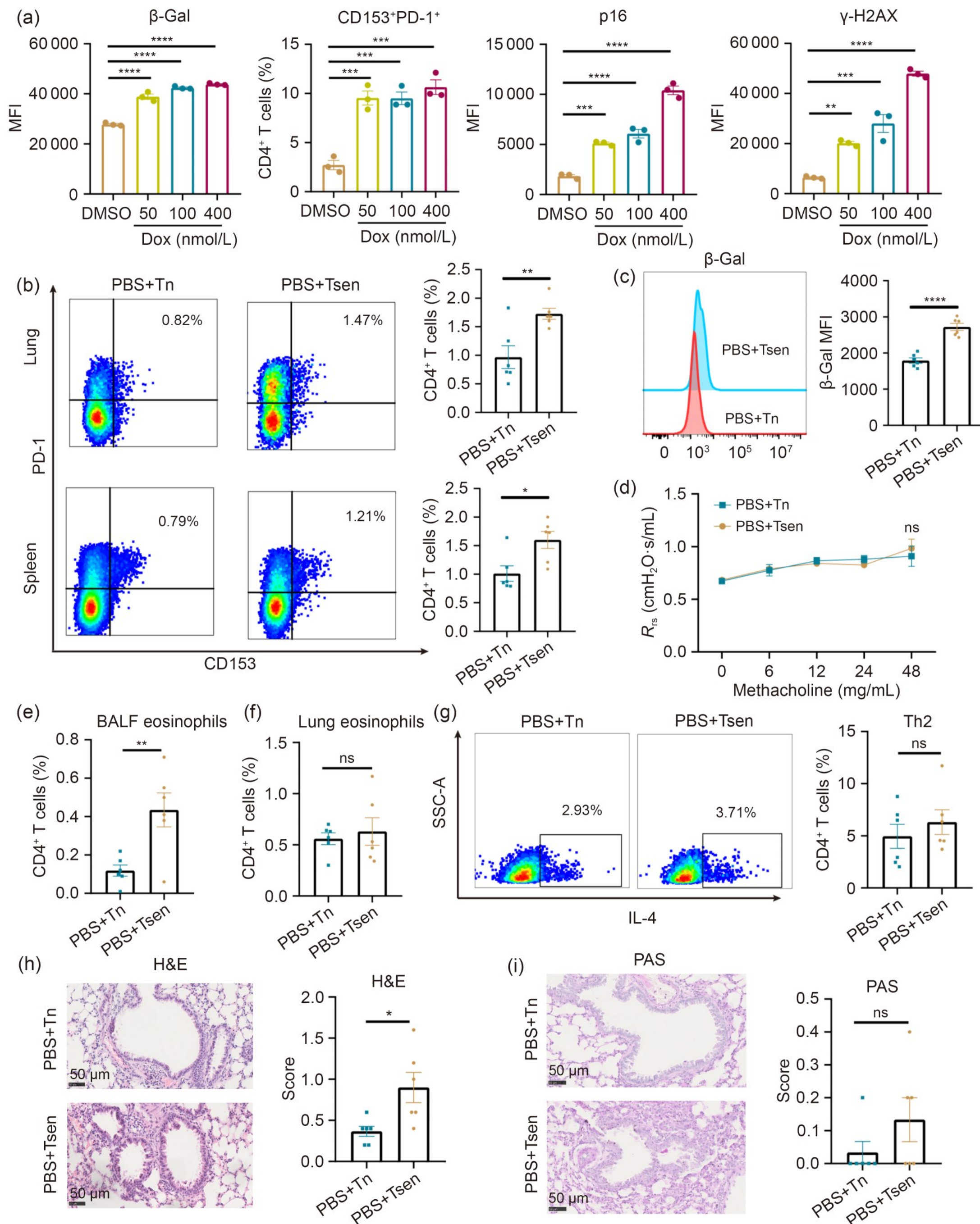

Fig. 5 Failure to induce spontaneous asthma onset by adoptive transfer of cluster of differentiation 4-positive ($CD4^+$) senescent T cells (Tsens) in healthy mice. (a) Senescence-inducing effect of doxorubicin (Dox) at different concentrations in $CD4^+$ T cells (*n*=3). (b, c) Representative flow cytometry plots and statistical analysis of the percentages of $CD153^+PD\text{-}1^+CD4^+$ Tsens in mouse lungs and spleens (*n*=6), and the mean fluorescence intensity (MFI) of senescence-associated β-galactosidase (SA-β-Gal) activity in lung $CD4^+$ T cells (*n*=6). (d) Total resistance of the respiratory system (R_{rs}) in mice (*n*=6) treated with increasing concentrations of methacholine (0–48 mg/mL). Statistical significance was assessed in comparison to the Tn group. 1 cmH_2O=98.0665 Pa. (e, f) Statistical analysis of the percentages of eosinophils in the bronchoalveolar lavage fluid (BALF) (e) and lungs (f) of the mice (*n*=6). (g) Representative flow cytometry plots and statistical analysis of the percentages of T helper type 2 (Th2) cells in the mouse lungs (*n*=6). (h, i) Representative images and statistical analyses of hematoxylin and eosin (H&E)- and periodic acid-Schiff (PAS)-stained lung sections from each group (*n*=6). The bars show the means with standard errors of the means. $^*P$<0.05; $^{**}P$<0.01; $^{***}P$<0.001; $^{****}P$<0.0001; ns (not significant), *P*>0.05. DMSO: dimethyl sulfoxide; γ-H2AX: phosphorylated histone H2AX at Ser139; PBS: phosphate-buffered saline; Tn: nonsenescent T cells; PD-1: programmed cell death protein 1; SSC-A: side scatter-area; IL-4: interleukin-4.

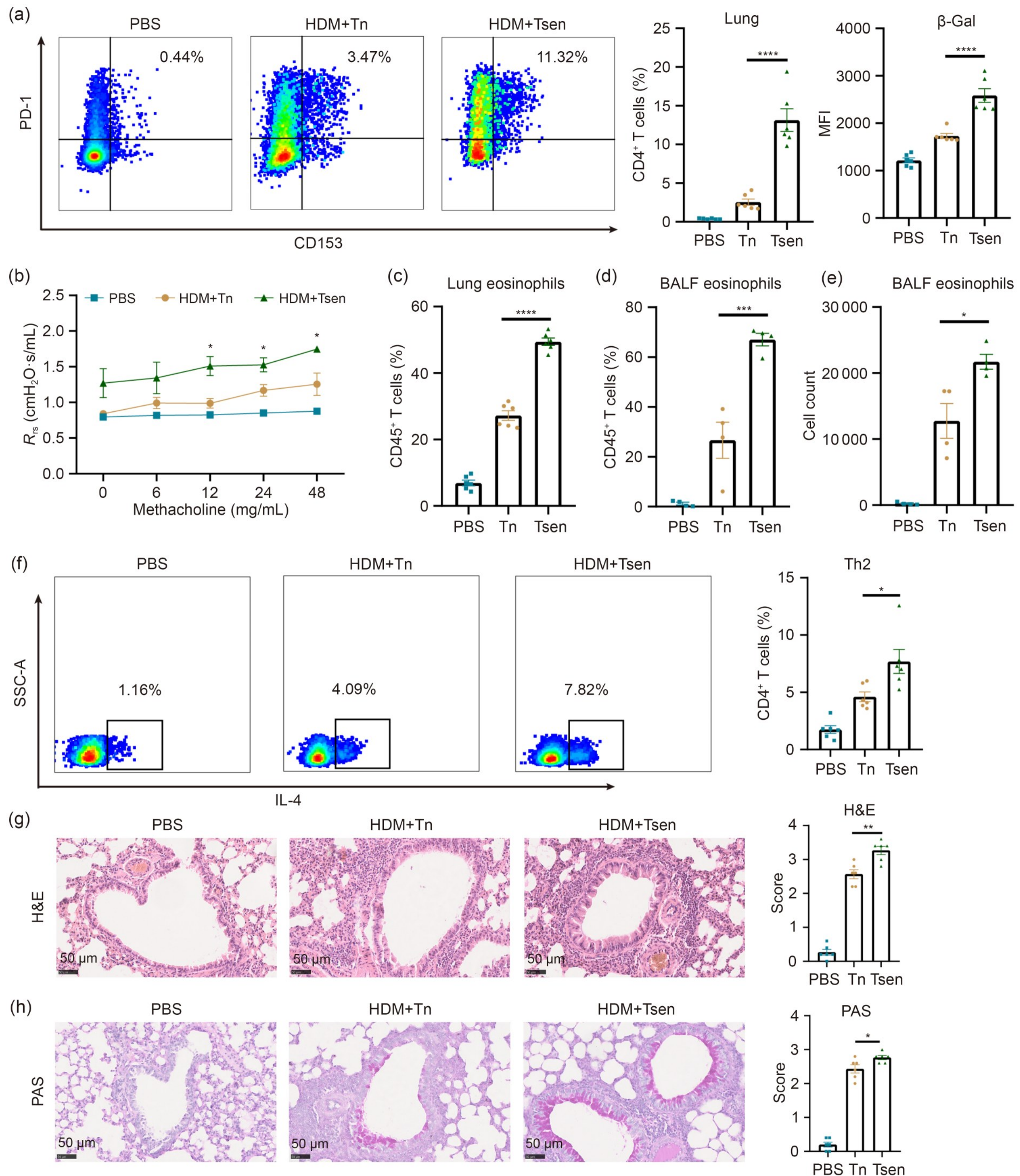

Fig. 6 Promotion of type 2 inflammation by adoptive transfer of cluster of differentiation 4-positive (CD4$^+$) senescent T cells (Tsens) in house dust mite (HDM)-treated mice. (a) Representative flow cytometry plots and statistical analysis of the percentages of CD153$^+$PD-1$^+$CD4$^+$ Tsens and the mean fluorescence intensity (MFI) of senescence-associated β-galactosidase (SA-β-Gal) activity in CD4$^+$ T cells in mouse lungs (*n*=6). (b) Total resistance of the respiratory system (R_{rs}) in mice (*n*=6) treated with increasing concentrations of methacholine (0–48 mg/mL). $^*P$<0.05, HDM+Tsen vs. HDM+Tn. 1 cmH_2O=98.0665 Pa. (c–e) Statistical analysis of the percentages of eosinophils in the lungs (c, *n*=6) and bronchoalveolar lavage fluid (BALF) (d) and the number of eosinophils in the BALF (e) of mice (*n*=4). (f) Representative flow cytometry plots and statistical analysis of the percentages of T helper type 2 (Th2) cells in the lungs of the mice (*n*=6). (g, h) Representative images and statistical analyses of hematoxylin and eosin (H&E)- and periodic acid-Schiff (PAS)-stained lung sections from each group (*n*=6). The bars show the means with standard errors of the means. $^*P$<0.05; $^{**}P$<0.01; $^{***}P$<0.001; $^{****}P$<0.0001. PBS: phosphate-buffered saline; Tn: nonsenescent T cells; PD-1: programmed cell death protein 1; SSC-A: side scatter-area; IL-4: interleukin-4.

3 Discussion

T cells are crucial components of the immune system, and T-cell senescence is considered one of the key features of immune system senescence (Soma and Nagata, 2022). Studies have shown that long-term chronic inflammation accelerates T-cell senescence (Lambers et al., 2009; Shirakawa et al., 2016; Zhang et al., 2024): elevated numbers of $CD28^-$ Tsens have been observed in adults with chronic inflammatory diseases such as rheumatoid arthritis, COPD, and obesity (Lambers et al., 2009; Shirakawa et al., 2016; Bauer, 2020). However, the characteristics of T-cell senescence in asthma have not been studied in detail. In this study, we detected elevated proportions of $CD4^+CD57^+CD28^-$ Tsens (but not $CD8^+CD57^+CD28^-$ T cells) in the peripheral blood and sputum of asthma patients. These findings suggest that $CD4^+$ Tsens are more prevalent in asthma patients, especially in those with strong type 2 inflammation and poorly controlled asthma, than in age-matched healthy controls. Although the difference in $CD4^+$ T-cell senescence between the eosinophilic and non-eosinophilic asthma subgroups did not reach statistical significance, a trend toward higher senescence was noted in eosinophilic asthma. This apparent discrepancy with the significant increase observed in the high-FeNO group likely reflects the distinct biological nature of these biomarkers. Eosinophil counts—either in blood or sputum—are relatively static downstream indicators of inflammation that are susceptible to modulation by corticosteroids and other external factors (Wang et al., 2023). In contrast, FeNO serves as a dynamic, real-time marker of IL-13-mediated epithelial inflammation (Escamilla-Gil et al., 2022). FeNO levels are less affected by diurnal variation or recent medication use and may better capture the current inflammatory milieu (Pelletier et al., 2022; Yuda et al., 2025). Therefore, discordance between eosinophils and FeNO is not uncommon and has been well-documented in asthma phenotyping (Badar et al., 2020). Finally, our findings were corroborated in an HDM-induced mouse model of type 2 asthma, which also exhibited increased $CD4^+$ T-cell senescence in the inflamed airway. This alignment between human and animal data supports the broader relevance of T-cell senescence as a feature of type 2 inflammatory asthma.

Our study provides important evidence that $CD4^+$ T cells in patients with type 2 asthma are more susceptible to senescence. After analyzing the immune phenotypes of cells in the peripheral blood and airways in the context of asthma, we were unable to determine whether asthma induced $CD4^+$ T-cell senescence or whether $CD4^+$ Tsens contributed to the development of asthma. Therefore, we used an HDM-induced mouse model of asthma and found that even in young mice, asthmatic mice presented increased percentages of $CD4^+$ Tsens compared to the phosphate-buffered saline (PBS)-treated controls. Furthermore, neutralizing IL-4 with monoclonal antibodies confirmed the causal relationship between asthma and $CD4^+$ T-cell senescence. In chronic inflammatory diseases such as asthma, long-term antigenic stimulation can lead to continuous T-cell activation and proliferation. This repeated activation may induce telomere shortening and DNA damage, impair DNA repair mechanisms, and disrupt immune modulation, ultimately leading to $CD4^+$ T-cell senescence (Mittelbrunn and Kroemer, 2021).

In addition to chronic antigenic stress, the type 2 inflammatory cytokines involved in asthma may play a key role in promoting T-cell senescence. A study showed that IL-4 induces senescence in human renal carcinoma cell lines through the upregulation of p21 via the STAT6 and p38 MAPK pathways (Kim et al., 2013). Another study revealed that IL-4 induces senescence in salivary epithelial cells through the reactive oxygen species (ROS)/p38 pathway in patients with immunoglobulin G4 (IgG4)-related sialadenitis (Min et al., 2022). In this study, we observed that the percentage of $CD4^+$ Tsens in the lungs of IL-4-neutralized mice was significantly lower than that in the lungs of control mice, suggesting that type 2 inflammation contributes to $CD4^+$ T-cell senescence, with IL-4 acting as an important signaling molecule. We also confirmed the roles of IL-4 and other type 2 inflammatory cytokines in inducing human $CD4^+$ T-cell senescence in vitro. Furthermore, we examined the signaling pathways involved in IL-4-induced senescence. Although both STAT6 and p38 MAPK were significantly activated in the lungs of HDM-treated mice, neutralization of IL-4 inhibited p38 MAPK activation but had no effect on STAT6 expression.

We also explored the impact of $CD4^+$ Tsens on asthma. Previous studies have shown that $CD4^+$ Tsens impair immune functions such as antiviral responses (Zhang et al., 2025). In asthma, type 2 inflammation promotes $CD4^+$ T-cell senescence, and the generated senescent cells secrete inflammatory cytokines, such as

IL-1β, IL-6, IL-8, and IFN-γ, contributing to chronic inflammation (Yang et al., 2023). The SASP has been observed in elderly asthma patients and in mouse models of allergic airway inflammation (Busse et al., 2007, 2017; Busse and Mathur, 2010; Judge et al., 2020). In this study, we performed adoptive transfer of $CD4^+$ Tsens and found that while the infusion of $CD4^+$ Tsens did not induce spontaneous asthma, it exacerbated type 2 inflammation in asthmatic mice. These findings suggest that targeting $CD4^+$ Tsens could represent a novel therapeutic approach for type 2 asthma. Our study also addresses the challenge of obtaining sufficient numbers of senescent cells from asthma patients and mice. To overcome this limitation, we induced senescence in $CD4^+$ T cells in vitro using Dox. We found that Dox-induced $CD4^+$ Tsens presented many typical features of senescence, but they did not fully recapitulate the characteristics of $CD4^+$ Tsens observed in asthma. Therefore, we plan to explore the adoptive transfer of sorted $CD4^+$ T cells expressing $CD153^+$ and $PD\text{-}1^+$ from mice in future studies.

Type 2 asthma exacerbates $CD4^+$ T-cell senescence, initiating a vicious cycle of chronic inflammation. Consequently, targeting $CD4^+$ Tsens could be an effective asthma treatment strategy. Currently available anti-senescence therapies, such as senomorphic and senolytic approaches, focus on targeting SASP signals to inhibit or neutralize the production of harmful SASP components or eliminate senescent cells that release these factors (Gasek et al., 2021). Drugs targeting specific senescent cell types are currently being evaluated, and senescent immune cells, particularly T cells, may be important therapeutic targets in type 2 asthma. We found that $CD153^+PD\text{-}1^+CD4^+$ senescent cell abundance was increased in asthmatic mice, and previous studies have shown that a vaccine targeting Tsens expressing CD153 could effectively improve glucose metabolism in obese mice (Yoshida et al., 2020; Mendelsohn and Larrick, 2022). Although CD153 has not been fully validated as a marker of $CD4^+$ Tsens in humans, applying antisenescence therapeutic strategies that target specific markers of $CD4^+$ Tsens has significant potential for the treatment of type 2 asthma.

One limitation of this study is the relatively small and imbalanced sample size between asthma patients and healthy controls, particularly in the sputum cohort, due to the invasive nature of sputum induction. To address this, we are continuing to collect clinical samples to expand the cohort, which will enable more refined subgroup analyses. Future studies with larger samples and integrated biomarker profiling will be important to validate and extend our findings. Another limitation is the lack of significant differences in $CD4^+$ T-cell senescence between eosinophil-defined asthma subgroups. While this may appear inconsistent with the elevated senescence in the high-FeNO group, it likely reflects differences in biomarker sensitivity. Eosinophil counts are downstream and easily influenced by corticosteroids, while FeNO better captures dynamic, IL-13-driven epithelial inflammation. Longitudinal studies using multiple biomarkers, such as FeNO, eosinophils, and IL-13, will help clarify the relationship between type 2 inflammation and T-cell senescence.

4 Conclusions

In this study, we demonstrated that individuals with asthma have a greater proportion of $CD4^+$ Tsens than healthy controls do and that the increase in $CD4^+$ Tsen abundance in asthma patients is likely mediated by type 2 inflammation. Blockade of IL-4 significantly reduced the proportion of $CD4^+$ Tsens in asthmatic mice. Moreover, adoptive transfer of $CD4^+$ Tsens did not induce spontaneous asthma but exacerbated type 2 inflammation. These findings highlight the therapeutic potential of targeting $CD4^+$ Tsens as a novel strategy for managing type 2 asthma.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Data availability statement

The data presented in this study are available from the corresponding author upon reasonable request.

Acknowledgments

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Author contributions

Huan LIU performed the methodology, investigation, data curation, and writing – original draft. Zemin LI performed the investigation. Yongchang SUN contributed to the methodology and writing – review & editing. Abudureyimujiang AILI contributed to the supervision and validation. Chun CHANG contributed to the conceptualization and supervision. All the authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Huan LIU, Zemin LI, Yongchang SUN, Abudureyimujiang AILI, and Chun CHANG declare that they have no conflicts of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (the Medical Science Research Ethics Committee of the Peking University Third Hospital, approval No. M2023075) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants for being included in the study. Additional informed consent was obtained from all participants for whom identifying information is included in this article. All animal experiments were approved by the Institutional Animal Care and Use Committee of Peking University Health Science Center (No. PUIRB-LA2022692).

Declaration on the use of generative AI tools

During the preparation of this work, the authors used ChatGPT to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Supplementary information

Materials and methods; Tables S1–S4; Figs. S1–S4