Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Bronchial epithelial cells are actively involved in initiating, maintaining, and regulating both innate and adaptive immune responses in the airways.\textsuperscript{1,2} Activated bronchial epithelial cells can produce a variety of inflammatory mediators that serve in a paracrine or autocrine manner to regulate airway inflammation.\textsuperscript{3,5} IL-27 is a pleiotropic cytokine consisting of EBI3 and p28 subunits.\textsuperscript{6} It is an early product of activated antigen-presenting cells stimulated by toll-like receptor ligands or infectious agents.\textsuperscript{7,9} IL-27 could drive the differentiation of the T helper (Th) cell type 1 (Th1) subset in the early stage of development,\textsuperscript{6,8} and support germinal center function by enhancing IL-21 production and the function of follicular Th cells.\textsuperscript{10} IL-27 is able to stimulate monocytes, mast cells, and keratinocytes to produce a variety of proinflammatory cytokines.\textsuperscript{9,11} In addition, IL-27 exhibits anti-tumor activity by promoting effector responses of CD8\textsuperscript{+} T cells and natural killer cells.\textsuperscript{12,13} On the other hand, IL-27 plays an immunoregulatory role in suppressing the development of the Th1, Th2, and

\textbf{Background:} The role of IL-27 in the pathogenesis of airway inflammatory diseases remains elusive. We, therefore, have studied its concentrations in the sputum and plasma of patients with COPD and patients with pulmonary TB (PTB), and further investigated the mechanism-of-action effects of IL-27 on bronchial epithelial cells in vitro.

\textbf{Methods:} Human bronchial epithelial cells grown on air-liquid interface culture were activated by IL-27, alone, or in combination with other inflammatory cytokines in the presence or absence of various signaling molecule inhibitors. The expression of CXCL10 was detected by reverse transcription polymerase chain reaction and enzyme-linked immunosorbent assay (ELISA). The underlying signaling pathways were studied by intracellular staining using flow cytometry, Western blot, ELISA, or siRNA.

\textbf{Results:} Significantly higher sputum and plasma concentrations of IL-27 were found in patients with COPD (n = 34; $P < .01$ and $P < .001$, respectively) or patients with PTB (n = 31; $P < .01$ and $P < .001$, respectively) than in healthy control subjects (n = 48). Sputum, but not plasma, IL-27 levels in patients with COPD correlated negatively with FEV\textsubscript{1} ($r = -0.51$, $P < .01$). Sputum, but not plasma, IL-27 in patients with PTB correlated positively with mycobacterial load in sputum ($r = 0.48$, $P < .05$). Further in vitro studies demonstrated that IL-27 could induce gene and protein expression of CXCL10 in bronchial epithelial cells, which was regulated by the activation of the phosphatidylinositol 3-OH kinase (PI3K)-Akt signaling pathway.

\textbf{Conclusions:} The production of IL-27 is related to the pathogenesis of COPD and PTB, and IL-27 induces the expression of CXCL10 in bronchial epithelial cells through the activation of the PI3K-Akt signaling pathway.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{A schematic representation of the signaling pathways involved in IL-27's effects on bronchial epithelial cells.}
\end{figure}

\textbf{Abbreviations:} ELISA = enzyme-linked immunosorbent assay; IFN = interferon; PBEC = primary human bronchial epithelial cell; PI3K = phosphatidylinositol 3-OH kinase; PTB = pulmonary TB; Th = T helper; TNF = tumor necrosis factor
Th17 cell subsets and driving the expansion of inducible regulatory T cells to produce antiinflammatory cytokine IL-10. 7,8,14 Inflammatory cells, such as macrophages and dendritic cells, represent highly active cells that increase in the airways of patients with inflammatory diseases such as COPD and pulmonary TB (PTB). 15-17 Because activated macrophages and dendritic cells are the main sources of IL-27, 7 there might be an aberrant production of IL-27 in patients with COPD and PTB. However, its immunopathologic role in airway inflammation and its relationship to airway inflammatory diseases have not yet been elucidated. The aim of this study was to investigate IL-27 production in sputum and plasma obtained from patients with COPD and patients with PTB and to study how it activates human bronchial epithelial cells in airway inflammatory diseases.

**Materials and Methods**

**Subjects**

Patients and healthy smoking and nonsmoking control subjects were enrolled in this study. Patients with COPD were diagnosed using the criteria of the GOLD (Global Initiative for Chronic Obstructive Lung Disease). Patients with COPD who had an exacerbation during the 3 months prior to the visit were excluded. Patients with COPD who had used corticosteroids, theophylline, long-acting β2-agonists, leukotriene antagonists, or antihistamines within the 3 months prior to the study were excluded, as were subjects who had histories of respiratory tract infection within the previous 2 months. The patients with PTB presented a clinical manifestation typical for *Mycobacterium tuberculosis*, which includes radiologic analysis, sputum smears, and culture positivity confirmed by bacteriologic examination. All patients with PTB were newly diagnosed, and no patient was treated with antiinflammatory drugs such as nonsteroidal antiinflammatory drugs, steroids, or others. The protocol described here was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (approval No. 20080156), and informed consent was obtained from all participants according to the Declaration of Helsinki.

**Sputum and Blood Sampling**

Sputum was induced and taken according to the protocols described previously. 18 Ethylenediaminetetraacetic acid venous peripheral blood was also collected to obtain plasma. All sputum and plasma were stored at −80°C until analysis. The duration of time between sputum or plasma sampling and protein analysis of patient samples was ≤2 months.

**Reagents**

Recombinant human IL-1β, IL-4, IL-6, IL-12, IL-13, IL-17F, IL-23, IL-27, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α were purchased from R&D Systems. Inhibitor k-b-α phospholipase A2 inhibitor BAY11-7082, extracellular signal-regulated kinase inhibitor U0126, c-Jun N-terminal kinase inhibitor SP600125, p38 mitogen-activated protein kinase inhibitor SB203580, phos- phatidylinositol 3-OH kinase (PI3K) inhibitor LY294002, and Janus kinase inhibitor AG490 were purchased from Calbiochem Corp. PI3K p110α inhibitor AS604850 and PI3K p110β inhibitor IC87114 were purchased from Merck Biosciences. In all studies, the concentration of dimethyl sulfoxide was 0.1% (vol/vol).

**Human Bronchial Epithelial Cell Culture**

Primary human bronchial epithelial cells (PBECs) were purchased from ScienCell Research Laboratories and cultured in bronchial epithelial cell growth medium as described previously. 19 BEAS-2B cells were obtained from the American Type Culture Collection, and they were used instead of PBEC for efficient transfection.

**Gene Expression of CXCL10**

The levels of CXCL10 gene expression were quantified by calculating the ratio of densitometric readings of the band intensity for CXCL10 and G3PDH from the same complementary DNA sample.

**Enzyme-linked Immunosorbert Assay**

The concentrations of IL-27, CXCL8, and IFN-γ were quantitated by enzyme-linked immunosorbent assay (ELISA) reagents from R&D Systems. CXCL10 levels in the supernatants and cell lysates were quantitated by a commercially available ELISA kit (Biosource), according to the manufacturer’s instructions, and expressed as the amount recovered per 10^6 cells. The P13K activity was also detected using an ELISA kit (Echelon Biosciences).

**Analysis of Activated Intracellular Signaling Molecules**

For flow cytometric analysis, permeabilized PBEC were stained with mouse antihuman phosphorylated Akt (BD Pharmingen) and phosphorylated P3K (Cell Signaling Technology) or mouse IgG1 antibodies (BD Pharmingen), followed by fluorescein isothiocyanate-conjugated goat antimouse secondary antibodies. The expression of intracellular phosphorylated signaling molecules was then analyzed by flow cytometry (FACSCalibur, BD Biosciences). Western blot analysis of activated signaling molecules was performed as described previously. 20

**Knockdown of Gene Expression With siRNA**

P13K p110α, P13K p110β, Akt, and control siRNA were purchased from Cell Signaling Technology, BEAS-2B cells purchased from Cell Signaling Technology. (approval No. 20080156), and informed consent was obtained from all participants according to the Declaration of Helsinki.
Table 1—Sequences of Primers and Predicted Sizes for Target Genes

| Chemokine/Primer | Predicted Size (Base Pairs) |
|------------------|-----------------------------|
| CXCL10           |                             |
| Forward          | 5'-TGAATCAAAGCGGATCTCTG-3'  | 275 |
| Reverse          | 5'-TTTCTTCGTCACTCGTTTCCAG-3'|
| G3PDH            |                             |
| Forward          | 5'-ACCACAGTCCATGCCATCAC-3'  | 450 |
| Reverse          | 5'-TCCACCCACCCCTGTTGCTGA-3' |

The amplification reaction was performed for 30 cycles, with denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 30 s.

were transfected with 25 nM each of siRNA with 5 μL of Lipofectamine 2000 (Promega), and grown in F12/Dulbecco modified Eagle medium with 10% fetal bovine serum without antibiotics for 24 h. The cells and cell supernatants were then harvested after stimulation with IL-27, and subjected to Western blot or ELISA analysis.

Statistical Analysis

All data were expressed as mean ± SD. Differences between groups were assessed by Kruskal-Wallis test, Mann-Whitney U test, Student t test, or one-way analysis of variance with Bonferroni post hoc test. Non-parametric Spearman rank correlation coefficient was used to test correlations between two parameters. P < .05 was considered significantly different.

RESULTS

Sputum and Plasma IL-27 in Patients With COPD and Patients With PTB

A total of 113 subjects (34 smokers with COPD, 31 nonsmokers with PTB, 26 healthy smokers, and 22 healthy nonsmokers) were recruited for this study, and the clinical characteristics of the subjects are summarized in Table 2. The concomitant medications for COPD were inhaled corticosteroids (21 patients), long-acting muscarinic antagonists (18 patients), and long-acting β2-agonists (19 patients). No patients with COPD were receiving systemic corticosteroid therapy. The newly diagnosed patients with PTB were treated with a standard short-course anti-TB chemotherapy consisting of isoniazid, rifampin, pyrazinamide, and ethambutol.

Compared with healthy nonsmokers or smokers with normal lung function, sputum IL-27 was significantly elevated in patients with COPD (P < .01) and patients with PTB (P < .01) (Fig 1A). In addition, the levels of plasma IL-27 in patients with COPD and patients with PTB were significantly elevated compared with those of healthy nonsmokers (P < .001) and healthy smokers (P < .001) (Fig 1B). However, there was no significant correlation between sputum and plasma IL-27 levels in patients with COPD or those with PTB (data not shown).

Five patients with COPD and six patients with PTB were recruited after treatment for 8 weeks, and sputum concentrations of IL-27 showed reproducibility and the percentage change in IL-27 values was ± 10% in patients with COPD (Fig 1C). However, sputum IL-27 levels decreased in all six patients with PTB by week 8, and the percentage change in IL-27 levels was > 30% (Fig 1D). IL-27 levels in plasma showed kinetics similar to those observed in sputum (data not shown).

Association Between Sputum IL-27 and Lung Function in COPD and PTB

Sputum IL-27 concentrations in patients with COPD were negatively correlated with FEV1 % predicted (r = −0.51, P < .01) (Fig 1E). However, IL-27 was not correlated with residual volume/tot al lung capacity (r = 0.06) (Fig 1F). No significant correlation...
Figure 1. IL-27 concentrations in induced sputum and plasma were measured by dual antibody sandwich enzyme-linked immunosorbent assay. A standard curve was generated by using known amounts of recombinant human IL-27. Each sample was tested in duplicate and the concentrations were determined from the standard curve. **P < .01, ***P < .001, when compared between groups denoted by horizontal lines. A, Induced sputum. B, Plasma. Patients with COPD and patients with PTB were recruited after 8 weeks of treatment to investigate the concentrations of IL-27. C, Five patients with COPD. D, Six patients with PTB. E, Correlation between sputum IL-27 and FEV1 % predicted in patients with COPD. F, Correlation between sputum IL-27 and RV/TLC in patients with COPD. G, Correlation between sputum IL-27 and mycobacterial load (as assessed by log CFU) in induced sputum by quantitative mycobacterial culture. The nonparametric Spearman rank correlation test was used to test correlations between two parameters. CFU = colony forming unit; PTB = pulmonary TB; RV = residual volume; TLC = total lung capacity.
was detected between sputum IL-27 and sputum CXCL8 in patients with COPD \((r = 0.40)\) (data not shown). In addition, plasma IL-27 was not correlated with any clinical indices, such as smoking status and lung function tests (data not shown). In patients with PTB, a positive correlation was observed between sputum IL-27 levels and mycobacterial load (as assessed by log CFU) in induced sputum \((r = 0.48, P < .05)\) (Fig 1G). However, there was no detectable correlation between plasma IL-27 levels and mycobacterial load in induced sputum \((r = 0.25)\) (data not shown). In addition, no significant correlation was detected between sputum IL-27 levels and sputum IFN-\(\gamma\) \((r = 0.32)\) (data not shown).

**Effects of IL-27 on CXCL10 Expression in PBEC:**
As shown in Figures 2A and 2B, IL-27 could induce CXCL10 gene expression in PBEC time dependently and dose dependently. In addition, the protein levels of CXCL10 in cell lysates were significantly increased, and peaked at the 12-h time point after stimulation with 10 and 100 ng/mL of IL-27 (Fig 2C), whereas the levels of CXCL10 in the supernatants peaked at 24 h and decreased at 48 h after stimulation (Fig 2D). However, IL-27 could not induce the expression of IL-6, TNF-\(\alpha\), or CXCL8 in PBEC (data not shown).

**IL-27 Augments the Production of CXCL10 in Cytokine-Treated PBEC**

As shown in Figure 3, stimulation of PBEC with each of the five cytokines IL-27, IFN-\(\gamma\), IL-1\(\beta\), TNF-\(\alpha\), and IL-17F induced the production of CXCL10. However, IL-4 and IL-13 and other IL-6/IL-12 family cytokines, including IL-6, IL-12, and IL-23, could not activate PBEC to express CXCL10. Furthermore, the combination of IL-27 and each of the four cytokines (IFN-\(\gamma\), IL-1\(\beta\), TNF-\(\alpha\), and IL-17F) significantly augmented CXCL10 production in comparison with that observed in PBEC activated by IL-27.

**Effects of Signaling Molecule Inhibitors on IL-27-induced CXCL10 Production**

The cytotoxicities of signaling molecule inhibitors on PBEC have been determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
IL-27 could induce the phosphorylation of PI3K (Fig 5A) and Akt (Fig 5B) by intracellular fluorescence staining using flow cytometry. PI3K-Akt activation was highly reproducibly detectable in PBEC in response to IL-27 by means of ELISA and Western blot analyses (Fig 5C, 5D).

siRNA-PI3K p110α, siRNA-PI3K p110β, and siRNA-Akt Suppressed IL-27-Induced CXCL10 Expression

BEAS-2B cells were transfected with siRNA specific for PI3K p110α, PI3K p110β, and Akt, and Western blot analysis showed that the expression of PI3K p110α and PI3K p110β was completely inhibited by PI3K p110α- and PI3K p110β-specific siRNA, respectively (Fig 6A, 6B). In addition, the phosphorylation of Akt was significantly reduced by knockdown of PI3K p110α (by about 85%) and PI3K p110β (by about 70%) (Fig 6C).

As shown in Figures 6D and 6E, the induction of CXCL10 gene and protein expression by IL-27 was significantly inhibited in BEAS-2B cells transfected with siRNA for PI3K p110α, PI3K p110β, and Akt.

**Discussion**

In this study, we demonstrated for the first time that sputum and plasma levels of IL-27 were significantly elevated in COPD and PTB patients compared with...
enhance the expression of intercellular adhesion molecule 1 on the surface of bronchial epithelial cells, we took bronchial epithelial cells as an in vitro cell model to study the potential role of IL-27 in the induction of cytokine and chemokine in bronchial epithelial cells. We found that IL-27 was able to induce the expression of CXCL10 but not IL-6, TNF-α, or CXCL8, which is consistent with previous reports that IL-27 could stimulate the production of CXCL10 in monocytes, keratinocytes, and fibroblast-like synoviocytes. In fact, CXCL10 is a pivotal chemokine that contributes to both Th1- and Th2-type airway inflammation and a significantly increased production of CXCL10 has been seen in airway inflammatory diseases such as COPD, PTB, chronic bronchitis, and severe acute respiratory syndrome. In this study, we found that IL-27 is a novel inducer of healthy control subjects. In addition, sputum, but not plasma, IL-27 concentrations in COPD showed a significant correlation with FEV₁, suggesting a possible link to disease severity. However, sputum IL-27 was not correlated with residual volume/total lung capacity, indicating that IL-27 may not be associated with alveolar wall destruction in COPD. In addition, sputum, but not plasma, IL-27 was correlated with mycobacterial load in sputum in patients with PTB, suggesting that IL-27 in sputum may reflect the intensity of TB infection. Additional COPD and PTB patients are currently being recruited to further evaluate the sputum and plasma conversion of IL-27 and the response to antiinflammation therapies.

Because bronchial epithelial cells are central participants in the pathogenesis of airway inflammatory diseases and we have recently found that IL-27 could enhance the expression of intercellular adhesion molecule 1 on the surface of bronchial epithelial cells, we took bronchial epithelial cells as an in vitro cell model to study the potential role of IL-27 in the induction of cytokine and chemokine in bronchial epithelial cells. We found that IL-27 was able to induce the expression of CXCL10 but not IL-6, TNF-α, or CXCL8, which is consistent with previous reports that IL-27 could stimulate the production of CXCL10 in monocytes, keratinocytes, and fibroblast-like synoviocytes. In fact, CXCL10 is a pivotal chemokine that contributes to both Th1- and Th2-type airway inflammation and a significantly increased production of CXCL10 has been seen in airway inflammatory diseases such as COPD, PTB, chronic bronchitis, and severe acute respiratory syndrome. In this study, we found that IL-27 is a novel inducer of

Figure 4. Effects of different signaling molecule inhibitors on IL-27-induced CXCL10 production in PBECs grown on air-liquid interface culture. A, The effects of AG, BAY, LY, SB, or U on IL-27-induced CXCL10 release. B, Selective inhibition of pan-phosphatidylinositol 3-OH kinase (PI3K), PI3K p110γ, or PI3K p110α activity on IL-27-induced CXCL10 release. PBECs were pretreated with AG (5 μM), BAY (0.8 μM), LY (0.5-10 μM), SB (20 μM), U (10 μM), AS (1-5 μM), or IC (1-5 μM) for 1 h, followed by incubation for a further 24 h with or without IL-27 (100 ng/mL) in the presence of inhibitors. The release of CXCL10 was determined by enzyme-linked immunosorbent assay. DMSO (0.1%) was used as the vehicle control. Results are expressed as the arithmetic mean ± SD from three independent experiments. **P < .01, ***P < .001 when compared between groups denoted by horizontal lines. AG = AG490; AS = AS604850; BAY = BAY11-7082; CTL = medium control; DMSO = dimethyl sulfoxide; IC = IC87114; LY = LY294002; SB = SB203580; SP = SP600125; U = U0126. See Figure 2 legend for expansion of other abbreviation.
Regarding signaling pathways of IL-27, we demonstrated that IL-27-induced CXCL10 expression in bronchial epithelial cells is primarily regulated by the PI3K-Akt pathway. Furthermore, both PI3K p110α and PI3K p110β isoforms were important for IL-27-induced CXCL10 expression, whereas PI3K p110γ and PI3K p110δ had little effect. These results are reasonable because PI3K p110α and PI3K p110β are widely distributed, whereas PI3K p110γ and PI3K p110δ are enriched only in leukocytes. However, inhibition of the PI3K-Akt pathway could partially suppress the expression of CXCL10 induced by IL-27 in bronchial epithelial cells, suggesting that other unidentified signaling pathways might contribute to CXCL10 expression.

Taken together, our results provide evidence that IL-27 might play an important role in airway inflammatory diseases including COPD and PTB. IL-27 was found to induce the expression of chemokine CXCL10 in bronchial epithelial cells via the activation of the PI3K-Akt signaling pathway. Elucidating the interactions between IL-27 and CXCL10 may be important in understanding and treating airway inflammatory diseases.
Figure 6. Effects of siRNA-PI3K p110α, siRNA-PI3K p110β, and siRNA-Akt on IL-27-induced CXCL10 expression. BEAS-2B cells were transfected with or without siRNA-PI3K p110α and siRNA-PI3K p110β, and their blocking effects were validated by Western blot. A, Blocking effects on the expression of PI3K p110α. B, Blocking effects on the expression of PI3K p110β. C, Blocking effects on the phosphorylation of Akt. BEAS-2B cells were transfected with siRNA-PI3K p110α, siRNA-PI3K p110β, and siRNA-Akt. The cells and cell supernatants were then harvested at 2 h and 24 h, respectively, after stimulation with 100 ng/mL of IL-27. D, Level of CXCL10 gene expression measured by reverse transcription polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). E, Level of protein production measured by RT-PCR and ELISA. Results are expressed as the arithmetic mean ± SD from three independent experiments. *P < .05, **P < .01, and ***P < .001 when compared between groups denoted by horizontal lines. GADPH = glyceraldehyde 3-phosphate dehydrogenase. See Figure 1 and 5 legends for expansion of other abbreviations.

Acknowledgments

Author contributions: Dr Cao: contributed to the conception and design of the study; the acquisition, analysis, and interpretation of the data; and the drafting of the manuscript.

Dr Zhang: contributed to the conception and design of the study; the acquisition, analysis, and interpretation of the data; and the drafting of the manuscript.

Dr Li: contributed to the recruitment of subjects, the acquisition and interpretation of the data, and manuscript review.

Dr Xu: contributed to the recruitment of subjects, the acquisition and interpretation of the data, and manuscript review.

Dr Huang: contributed to the recruitment of subjects, the acquisition and interpretation of the data, and manuscript review.

Dr Xiang: contributed to the recruitment of subjects, the acquisition and interpretation of the data, and manuscript review.
REFERENCES

1. Khair OA, Davies RJ, Devalia JL. Bacterial-induced release of inflammatory mediators by bronchial epithelial cells. *Eur Respir J*. 1996;9(9):1913-1922.

2. Velden VH, Versnel HF. Bronchial epithelium: morphology, function and pathophysiology in asthma. *Eur Cytokine Netw.* 1998;9(4):555-597.

3. Martin LD, Rochelle LG, Fischer BM, Krunkosky TM, Adler KB. Airway epithelium as an effector of inflammation: molecular regulation of secondary mediators. *Eur Respir J*. 1997;10(9):2139-2146.

4. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. *J Allergy Clin Immunol*. 2007;120(6):1270-1284.

5. Kato A, Schleimer RP. Beyond inflammation: airway epithelial cells are at the interface of innate and adaptive immunity. *Curr Opin Immunol*. 2007;19(6):711-720.

6. Pflanz S, Timans JC, Cheung J, et al. IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4+ T cells. *Immunology*. 2002;16(6):779-790.

7. Villarino AV, Huang E, Hunter CA. Understanding the function and pathophysiology in asthma. *Eur Respir J*. 2004;173(2):715-720.

8. Hunter CA, Villarino A, Arts D, Scott P. The role of IL-27 in the development of T-cell responses during parasitic infections. *Immunol Rev*. 2004;202:106-114.

9. Wittmann M, Zeitvogel J, Wang D, Werfel T. IL-27 is expressed in chronic human eczematous skin lesions and stimulates human keratinocytes. *J Allergy Clin Immunol*. 2009;124(1):81-89.

10. Batten M, Ramamoorthi N, Kljavin NM, et al. IL-27 supports germinal center function by enhancing IL-21 production and the function of T follicular helper cells. *J Exp Med*. 2010;207(13):2895-2906.

11. Pflanz S, Hibbert L, Mattson J, et al. WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J Immunol*. 2004;172(4):2225-2231.

12. Mayer KD, Mohrs K, Reiley W, et al. Cutting edge: T-bet and IL-27R are critical for vivo IFN-gamma production by CD8 T cells during infection. *J Immunol*. 2008;180(2):693-697.

13. Matsu M, Kishida T, Nakano H, et al. Interleukin-27 activates natural killer cells and suppresses NK-resistant head and neck squamous cell carcinoma through inducing antibody-dependent cellular cytotoxicity. *Cancer Res.* 2009;69(6):2523-2530.

14. Stumhofer JS, Silver JS, Laurence A, et al. Interleukins 27 and 6 induce STAT3-mediated T cell proliferation of interleukin 10. *Nat Immunol*. 2007;8(12):1363-1371.

15. Pearl JE, Khader SA, Solache A, et al. IL-27 signaling compromises control of bacterial growth in mycobacteria-infected mice. *J Immunol*. 2004;173(12):7490-7496.

16. Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet*. 2009;374(9691):744-753.

17. González-Juarrero M, O’Sullivan MP. Optimization of inhaled therapies for tuberculosis: the role of macrophages and dendritic cells. *Tuberculosis (Edinb)*. 2011;91(1):86-92.

18. Ollivenstein R, Taha R, Minshall EM, Hamid QA. IL-4 and IL-5 mRNA expression in induced sputum of asthmatic subjects: comparison with bronchial wash. *J Allergy Clin Immunol*. 1999;103(2 pt 1):238-245.

19. Cao J, Wong CK, Yin Y, Lam CW. Activation of human bronchial epithelial cells by inflammatory cytokines IL-27 and TNF-alpha: implications for immunopathophysiology of airway inflammation. *J Cell Physiol*. 2010;223(3):788-797.

20. Cheung PF, Wong CK, Lam CW. Molecular mechanisms of cytokine and chemokine release from eosinophils activated by IL-17A, IL-17F, and IL-23: implication for Th17 lymphocytes-mediated allergic inflammation. *J Immunol*. 2008;180(8):5625-5635.

21. Wong CK, Cao J, Yin YB, Lam CW. Interleukin-17A activation on bronchial epithelium and basophils: a novel inflammatory mechanism. *Eur Respir J*. 2010;35(4):883-893.

22. Guzzo C, Che Mat NF, Gee K. Interleukin-27 induces a STAT13- and NF-kappaB-dependent proinflammatory cytokine profile in human monocytes. *J Biol Chem*. 2010;285(32):24404-24411.

23. Wittmann M, Zeitvogel J, Wang D, Werfel T. IL-27 is expressed in chronic human eczematous skin lesions and stimulates human keratinocytes. *J Allergy Clin Immunol*. 2004;124(4):181-89.

24. Medoff BD, Safty A, Tager AM, et al. IFN-gamma-inducible protein 10 (CXCL10) contributes to airway hyperreactivity and airway inflammation in a mouse model of asthma. *J Immunol*. 2002;168(10):5278-5286.

25. Pookkali S, Das SD. Augmented chemokine levels and chemokine receptor expression on immune cells during pulmonary tuberculosis. *Hum Immunol*. 2009;70(2):110-115.

26. Saetta M, Mariani M, Panina-Bordignon P, et al. Increased expression of the chemokine receptor CXCR3 and its ligand CXCL10 in peripheral airways of smokers with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;165(10):1404-1409.

27. Panzer P, Lafitte JJ, Tsiopoulos A, Hamid Q, Tulic ML. Marked up-regulation of T lymphocytes and expression of interleukin-9 in bronchial biopsies from patients with chronic bronchitis with obstruction. *Chest*. 2003;124(5):1909-1915.

28. Tang NL, Chan PK, Wong CK, et al. Early enhanced expression of interferon-inducible protein-10 (CXCL10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. *Clin Chem*. 2005;51(12):2333-2340.

29. Kawaguchi M, Kokubu F, Huang SK, et al. The IL-17F signaling pathway is involved in the induction of IFN-gamma-inducible protein 10 in bronchial epithelial cells. *J Allergy Clin Immunol*. 2007;119(6):1408-1414.

30. Safty A, Dziejman M, Taha RA, et al. The T cell-specific CXC chemokines IP-10, Mig, and I-TAC are expressed by activated human bronchial epithelial cells. *J Immunol*. 1999;162(6):3549-3558.

31. Ali K, Camps M, Pearce WP, et al. Isoform-specific functions of phosphoinositide 3-kinases: p110 delta but not p110 gamma promotes optimal allergic responses in vivo. *J Immunol*. 2008;180(4):2538-2544.

32. Stoyanov B, Volinia S, Hanek T, et al. Cloning and characterization of a G protein-activated human phosphoinositide-3 kinase. *Science*. 1995;269(5245):690-693.

33. Vanhaesebroeck B, Wiegman MJ, Kotani K, et al. P110b, a novel phosphoinositide 3-kinase in leukocytes. *Proc Natl Acad Sci U S A*. 1997;94(9):4330-4335.