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Chemokine (C-X-C Motif) Ligand 12/Stromal Cell-Derived Factor-1 Is Associated With Leukocyte Recruitment in Asthma

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Background: Asthma is characterized by allergic airway inflammatory response involving extensive leukocyte infiltration. The stromal cell-derived factor (SDF)-1 or chemokine (C-X-C motif) ligand 12 (CXCL12) attracts a number of cells, including resting T lymphocytes, monocytes, CD34⁺ stem cells, basophils, and mature eosinophils. To date, however, the potential role of CXCL12/SDF-1 in relation to leukocyte recruitment in asthma has not been previously examined, to our knowledge.

Methods: Levels of CXCL12/SDF-1 in the BAL fluid (BALF) of 15 subjects with asthma and 13 healthy subjects were measured by enzyme-linked immunosorbent assay. Immunohistochemistry was performed to identify the cellular source of this chemokine.

Results: CXCL12/SDF-1 concentrations were significantly elevated in BALF from subjects with asthma compared with normal subjects (median 845 pg/mL, range, 296-1,700 pg/mL vs median 55 pg/mL, range 25-97 pg/mL; $P < .001$). Concentrations of CXCL12/SDF-1 correlated with macrophages ($r = 0.728$, $P < .01$), lymphocytes ($r = 0.651$, $P < .01$), and eosinophils ($r = 0.765$, $P < .01$). By immunohistochemistry, CXCL12/SDF-1 was localized to the airway epithelium and to a lesser extent to mononuclear cells.

Conclusion: CXCL12/SDF-1 is released in high concentration in BALF of patients with asthma. The finding that concentrations of this chemokine correlated with leukocyte numbers in BALF suggests that this chemokine may contribute to the cell recruitment in asthma.

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Abbreviations: BALF = BAL fluid; BM = bone marrow; CXCL12 = chemokine (C-X-C motif) ligand 12; CXCR4 = CXC chemokine receptor 4; IL = interleukin; ML = middle lobe; SDF = stromal cell-derived factor

Asthma is characterized by increased airway hyper-reactivity to physical, chemical, pharmacologic, and/or immunologic stimuli. The major clinical symptoms of asthma are the episodic occurrence of cough-

ing, dyspnea, wheezing, and chest tightness, alone or in combination. A common pathologic feature in asthma is the presence of a characteristic allergic airway inflammatory response involving extensive leukocyte infiltration, mucus overproduction, and airway hyperreactivity. The pathogenesis of allergic airway inflammation is complex, involving multiple cell types, such as T helper 2 cells, regulatory T cells, eosinophils, dendritic cells, mast cells, and parenchymal cells of the lung. The cellular response in allergic airway inflammation is controlled by a broad range

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of bioactive mediators, including IgE, cytokines, and chemokines.¹

The stromal cell-derived factor (SDF)-1 or chemokine (C-X-C motif) ligand 12 (CXCL12) is a member of the chemokine family, which consists of low-molecular-weight proteins (8-15 kD) produced by a variety of cells involved in the allergic inflammation.² The primary function of chemokines is to direct cellular traffic, stimulate chemotaxis of inflammatory cells, and induce cell surface integrins. CXCL12/SDF-1 is a chemokine with two isoforms: SDF-1 α , the predominant 89-amino acid protein form of SDF-1, and SDF-1 β , which contains an extension of four amino acids at the carboxyl terminus.² A third form of SDF (SDF-1 γ) was identified in rat that is identical to SDF-1 β , except for the insertion of 30 additional amino acids at the carboxyl terminus.³ Novel isoforms of CXCL12 have been identified.^{4,5} However, they exert weak leukocyte activity. CXCL12/SDF-1 binds to chemokine receptor 4 (CXCR4) and attracts a variety of cells, including resting T lymphocytes, monocytes, CD34⁺ stem cells, and mature eosinophils.⁶ CXCL12/SDF-1 also has different regulatory roles in several biologic processes, including cardiac and neuronal development, stem cell motility, neovascularization, angiogenesis, apoptosis, and tumorigenesis.⁷⁻¹¹ More recently, it has been reported that CXCL12/SDF-1 also signals through CXC chemokine receptor 7.¹² Evidence for a role of this chemokine in allergic inflammation derives from an animal study showing that the axis CXCL12/CXCR4 plays a pivotal role in the development of lung inflammation and airway hyperresponsiveness.¹³ Moreover, treating allergic mice with the CXCR4 antagonist AMD3100 was found to reduce airway hyperreactivity, peribronchial eosinophilia, and airway inflammation.¹⁴ Hoshino et al¹⁵ reported an increased immunoreactivity of CXCL12/SDF-1 in bronchial biopsies of subjects with asthma and suggested that positive cells could play a role in airway remodeling via angiogenesis. To date, however, the potential role of CXCL12/SDF-1 in relation to disease severity and cell recruitment in asthma has not been previously examined, to our knowledge.

MATERIAL AND METHODS

Subjects

A group of 15 symptom-free subjects with asthma treated with inhaled salbutamol alone and 13 healthy subjects volunteered to participate in the study. Atopic status was confirmed by skin-prick testing with different allergens (ie, mixed grass, tree pollen, dog and cat dander, cockroach, as well as *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) (AlkAbelló; Horsholm, Denmark). All the subjects were nonsmokers, without any other

pulmonary diseases. None was treated with oral corticosteroids or theophylline for at least 6 weeks before the participation in this study. Four subjects were receiving inhaled steroids (fluticasone propionate). Inhaled steroids were stopped 48 h before bronchoscopy. Clinical characteristics of subjects with asthma and normal subjects are shown in Table 1. The study was approved by the Instituto Nacional de Enfermedades Respiratorias Ethics Committee.

Bronchial Challenge Test (Methacholine Challenge Test)

Four days before the first bronchoscopy, subjects underwent baseline spirometry and bronchial reactivity testing. Bronchial reactivity was determined as previously described.¹⁶ After recording baseline FEV₁, subjects inhaled five breaths of 0.9% sodium chloride solution (saline) from an Inspiron nebulizer (CR Bard; Sunderland, England) via a mouthpiece. Measurements of FEV₁ were made at 1 and 3 min, and provided these values did not decrease by > 10% of baseline, the methacholine provocation was undertaken. Subjects inhaled increasing doubling concentrations (0.02-32 mg/mL saline) of methacholine (Sigma; Poole, Dorset, England), with FEV₁ measurements made 1 and 3 min after each inhalation. The stepwise methacholine inhalations continued until the FEV₁ had decreased by at least 20% of the post-saline value. The log concentration of methacholine was then plotted against the percentage change in FEV₁ from the post-saline baseline value, and the cumulative concentration causing a 20% decrease was derived by linear interpolation between the last two data points.

Bronchoscopy and BAL Fluid

Fiberoptic bronchoscopy was undertaken as previously described¹⁷ and in accordance with current National Heart, Lung, and Blood Institute guidelines.¹⁸ All subjects received 2.5 mg salbutamol by nebulization 15 min prior to the procedure and atropine 0.5 mg and midazolam 3 to 8 mg IV immediately beforehand. Oxygen was administered continuously via a nasal cannula, and oxygen saturation was monitored. The bronchoscope was wedged in the medial segment of the middle lobe (ML) after administration of topical anesthesia. BAL was performed with a total 160 mL of normal saline solution (8 $\times$ 20 mL) instilled into the ML. After completion of procedure, subjects were observed in the department for minimum of 3 h, and further nebulized salbutamol was given as necessary. To investigate the potential cellular source of CXCL12/SDF-1, bronchial biopsies were obtained from six subjects (three from subjects with mild to moderate asthma and three from healthy subjects) from the medial segment of the ML using FB-15C alligator biopsy forceps (Olympus Optical; Essex, England) as we have described previously.¹⁶

BAL fluid (BALF) was centrifuged at 250 g for 10 min at 4°C, cells were separated, and supernatant was stored at -70°C. To obtain differential cell counts, a 100- μ L aliquot of cells (4 $\times$ 10⁵ cells) was subjected to cytocentrifugation (Cytospin; Cytopro Wescor;

Table 1—Clinical Characteristics of Subjects

Characteristic	Subjects With Asthma	Control Subjects
Subjects, No.	15	13
Age, y	32 (22-51)	36 (18-41)
Sex, M:F	6:9	10:3
FEV ₁ , %	98 (88-110)	118 (101-128)
PC ₂₀ , mg/mL	1.7 (0.04-4.2)	> 32

Values expressed as median (range) unless otherwise indicated. PC₂₀ = cumulative concentration of methacholine causing a 20% decrease in FEV₁.

Syracuse, NY), air dried, and stained with Giemsa Diff-Quik II stain (Baxter Scientific Products; McGaw Park, IL). Three hundred cells per slide were counted in light microscopy.

Immunohistochemistry

Bronchial biopsies were fixed in paraformaldehyde and paraffin embedded. Immunohistochemistry for CXCL12 was performed by indirect immunoperoxidase staining as previously described.¹⁹ Briefly, 4 μ m-thickness sections were mounted on silane-coated glass slides. Endogenous peroxidase activity was blocked using a 3% hydrogen peroxide solution in methanol for 1 h. After washing the tissues were blocked with BSA 0.5% for 2 h at room temperature. Subsequently, biopsies were incubated with a specific anti-CXCL12/SDF-1 mAb (MAB350; R&D Systems, Inc.; Minneapolis, MN) overnight at 4°C (1:50 dilution). Negative control slides were incubated without monoclonal antibody. Detection was accomplished using the appropriate biotinylated secondary Ab and the Elite Vectastain avidin-biotin-horseradish peroxidase reagent followed by the chromogenic substrate diaminobenzidine tetrahydrochloride (Vector; Burlingame, CA). Sections were counterstained with hematoxylin.

CXCL12/SDF-1 Measurements

Measurement of CXCL12 in fivefold concentrated BALF was performed using a double-antibody solid-phase immunoassay in duplicate samples. Briefly, Nunc 96-well flat-bottom plates (Thermo Fisher Scientific; Rochester, NY) were coated overnight at 4°C with capture antibody CXCL12/SDF-1 monoclonal antibody (R&D Systems). Plates were washed three times with wash buffer (0.05% Tween 20 in phosphate-buffered saline, pH 7.4). Standard (CXCL12/SDF-1 recombinant; R&D Systems) or BALF of controls or patients was added and incubated for 2 h at 37°C. After three times washed, a detection antibody (CXCL12/SDF-1 biotinylated polyclonal antibody; R&D Systems) was added and incubated 2 h at room temperature and then washed. A streptavidin-horseradish peroxidase (R&D Systems) conjugate was added and incubated for 20 min. Plates were washed six times, and 100 μ L of 3,3',5,5'-tetramethylbenzidine substrate (Sigma) was added. The reaction was stopped by adding 0.5 M sulfuric acid; optical density was obtained at 450 nm with correction at 540 nm. Concentration of CXCL12/SDF-1 in samples was calculated from the standard curve and their values corrected by the initial fivefold concentration. The lower limit of detection was 25 pg/mL.

Statistics

The Mann-Whitney *U* test was used to compare the concentrations of CXCL12/SDF-1 and number of cells in BALF. Correlations were determined using Spearman rank order correlation test. A *P* value of < .05 was considered significant. Statistical analysis was performed using the SPSS 12.0 software for Windows (SPSS, Inc; Chicago, IL).

RESULTS

Clinical Findings

The median age for subjects with asthma and controls was 32 and 36 years old, respectively. Lung function data showed that subjects with asthma suffered from mild to moderate asthma. The FEV₁% (median) predicted in subjects with asthma and control subjects was 98% (range 88%-110%) and 118%,

(range 101%-128%), respectively. All subjects with asthma were atopic, whereas control subjects were nonatopic. Clinical data are shown in Table 1.

BALF and Cell Population

BAL was obtained from all 28 subjects taking part in the study. There was no significant difference in the volume of fluid recovered between subjects with asthma and normal subjects (77 ± 9 mL vs 82 ± 10 mL, *P* > .05). Differential cell counts in BALF showed that lymphocyte, eosinophil, and macrophage numbers were significantly elevated in subjects with asthma compared with control subjects (medians 3.4 vs 0.67×10^6 /mL, *P* < .001; 0.12 vs 0.04×10^6 /mL, *P* < .005; and 14.4 vs 9.6×10^6 /mL, *P* < .001, respectively) (Table 2). Similarly, total cell counts were found to be increased in subjects with asthma as compared with normal subjects, 20.2 vs 10.8 ($\times 10^6$ /mL), *P* < .001.

CXCL12/SDF-1 in BALF

Levels of CXCL12/SDF-1 determined by enzyme-linked immunosorbent assay showed that this cytokine was significantly increased in BALF from subjects with asthma compared with control subjects (median 845 pg/mL, range 296-1,700 pg/mL vs 55 pg/mL, range 25-97 pg/mL, *P* < .001) (Fig 1). Levels of CXCL12/SDF-1 in women with asthma and men with asthma were similar (median: 887 pg/mL and median: 783 pg/mL, respectively; *P* > .05).

Concentrations of CXCL12/SDF-1 in BALF correlated with several cell types, including macrophages (*r* = 0.728, *P* < .01) (Fig 2A), lymphocytes (*r* = 0.651, *P* < .01) (Fig 2B), and eosinophils (*r* = 0.765, *P* < .01) (Fig 2C). There was no correlation between CXCL12/SDF-1 and the provocative response to methacholine (*r* = 0.09, *P* = .72).

CXCL12/SDF-1 Immunoreactivity in Bronchial Biopsies

The potential cellular source of CXCL12/SDF-1 was investigated using the technique of immunohistochemistry applied to bronchial biopsies. Figure 3

Table 2—Differential and Total Counts in BAL Fluid ($\times 10^6$ /mL)

Cell Type	Subjects With Asthma	Controls
Macrophages	14.4 (12-22) ^a	9.6 (4.9-12.9)
Lymphocytes	3.4 (2.0-4.9) ^a	0.67 (0.33-1.4)
Neutrophils	0.9 (0.5-1.8) ^a	0.43 (0.13-0.61)
Eosinophils	0.12 (0-0.4) ^b	0.04 (0-0.43)
Epithelial cells	0.09 (0-0.5)	0.13 (0-0.75)
Total cells	20.2 (17.3-29.8) ^a	10.8 (5.5-16.7)

Values expressed as median (range).

^a*P* < .001.

^b*P* < .005.

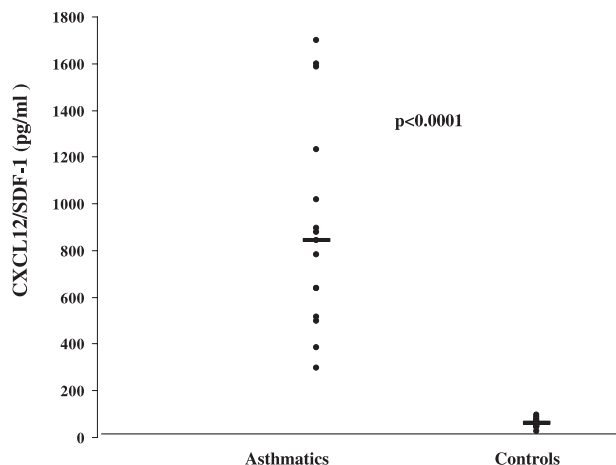


FIGURE 1. CXCL12/SDF-1 concentrations in BAL fluid of healthy controls and subjects with asthma. Horizontal bars show the median values. CXCL12 = chemokine (C-X-C motif) ligand 12; SDF-1 = stromal cell-derived factor-1.

shows bronchial tissue sections derived from two representative subjects with asthma stained with mAb anti-CXCL12/SDF-1 (Figs 3A, 3B) and without monoclonal antibody (Fig 3C); they show that CXCL12/SDF-1 was mainly localized to the airway epithelium (arrowhead) and sparse immunoreactivity localized to mononuclear cells (arrow) in the subepithelial tissue. Weaker CXCL12/SDF-1 immunoreactivity was seen in bronchial biopsies derived from normal subjects (Fig 3D).

DISCUSSION

This is first study showing that CXCL12/SDF-1 is released in high concentrations in the BALF of patients with asthma. Interestingly, levels of this chemokine correlated with the number of several leukocytes types, including lymphocytes, macrophages, and eosinophils, suggesting that CXCL12/SDF-1 may contribute to their recruitment into the airways of patients with asthma.

In 1996, CXCL12/SDF-1 was identified as a potent leukocyte attractant in the supernatants of murine bone marrow cell lines and shown to attract both human lymphocytes and monocytes.²⁰ Soon after, CXCR4 was identified as the receptor for this chemokine.²¹ The demonstration that this receptor functions as a coreceptor for the entry of T-tropic HIV viruses into CD4 cells initiated a broad research effort to elucidate the function of the CXCL12/CXCR4 axis. Interestingly, CXCL12/CXCR4 knock-out mice displayed a lethal phenotype characterized by deficient B-lymphopoiesis and myelopoiesis, as well as by abnormal neuronal and cardiovascular development,²² which led to the belief that this cytokine was predominantly involved in embryogen-

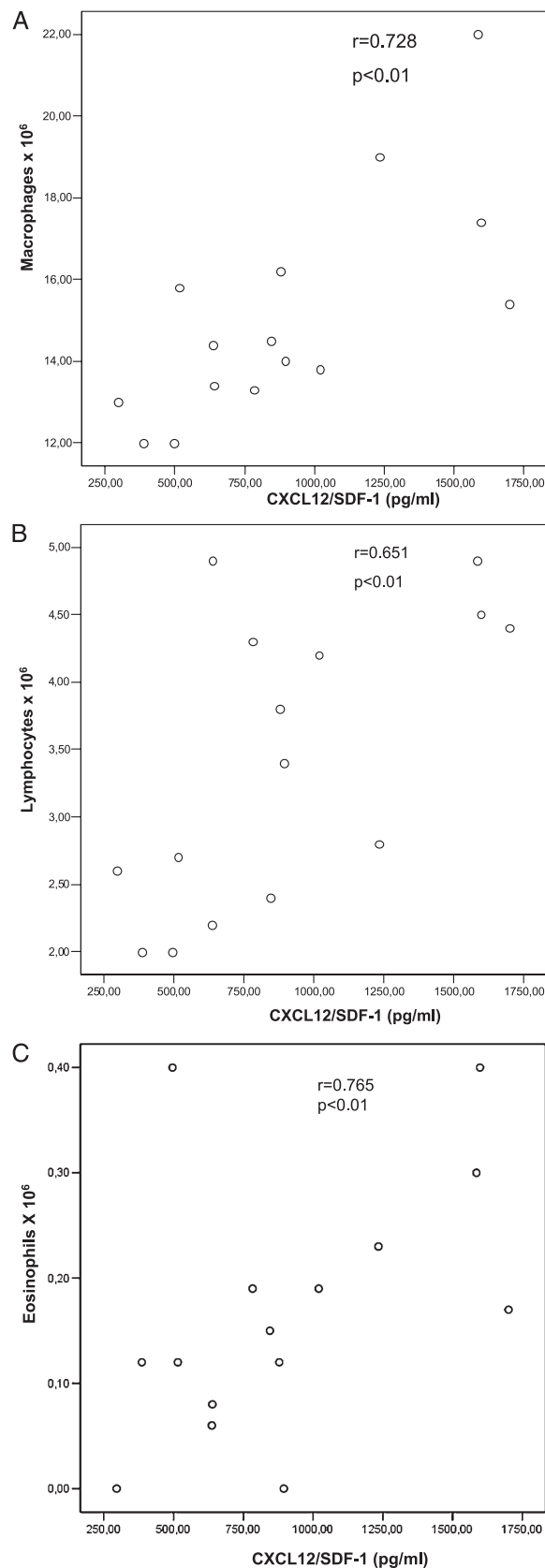


FIGURE 2. Correlation between CXCL12/SDF-1 levels and macrophages (A), lymphocytes (B), and eosinophils (C). See Figure 1 legend for expansion of abbreviations.

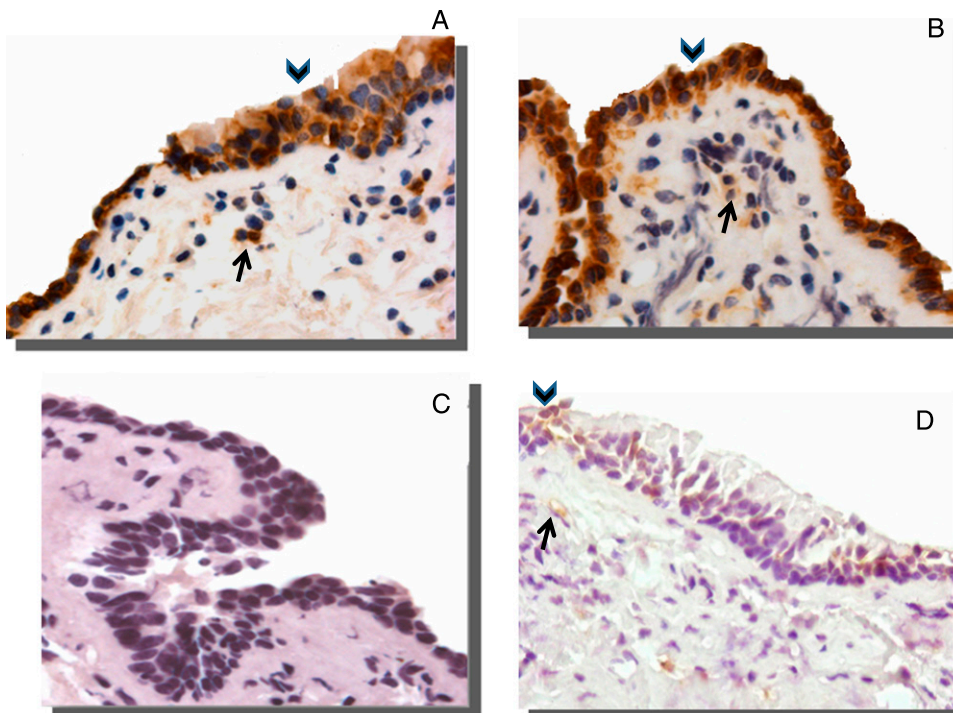


FIGURE 3. CXCL12/SDF-1 detected by immunohistochemistry in endobronchial biopsies from patients with asthma (A and B), control without monoclonal antibody (C), and subjects without asthma (D) (original magnification $\times 400$). Positive cells are stained with diaminobenzidine-peroxidase and hematoxyline counterstained. Arrowheads indicate epithelial cells. Arrows indicate mononuclear cells. See Figure 1 legend for expansion of abbreviations.

esis and in the trafficking of normal stem/progenitor cells. However, in 2000 Gonzalo et al¹³ reported that this chemokine was associated with the inflammatory process in a murine model of allergic inflammation. In 2003 Hoshino et al¹⁵ reported increased CXCL12/SDF-1 immunoreactivity in bronchial biopsies from patients with asthma and associated this chemokine with angiogenesis and airways remodeling. Nevertheless, no observations were made regarding the role of this chemokine in leukocyte recruitment.

The present study has shown that CXCL12/SDF-1 is released in high concentrations in BALF of subjects with asthma. Interestingly, levels of this chemokine were 15-fold higher compared with normal subjects. To investigate whether this chemokine could be associated with cell recruitment we sought correlations between this chemokine and the cells infiltrating the airways of patients with asthma. We found that CXCL12/SDF-1 concentration correlated with several cell types, including macrophages, eosinophils, and lymphocytes. This finding can be explained based on the fact that all these cells express CXCR4. To our knowledge, this is the first report that establishes a direct relationship between CXCL12/SDF-1 expression and cellular mobilization into the airways.

Because CXCL12/SDF-1 is constitutively produced in bone marrow (BM) it is tempting to hypoth-

esize that this chemokine may regulate cell trafficking early during the allergic inflammatory reaction. Indeed, Dorman et al²³ showed that allergen inhalation in patients with asthma induced both down-regulation of CXCR4 in BM CD34⁺ cells and reduction of BM CXCL12/SDF-1, facilitating the egress of progenitor cells to peripheral circulation by reducing progenitor cell retention to marrow stroma. Once within the circulation, progenitor cells may be redirected toward the inflammatory site by circulating chemokines. The finding that CXCL12/SDF-1 is produced in high concentrations into the asthmatic airways suggests that this cytokine may participate in the recruitment of CXCR4-bearing cells, including lymphocytes, macrophages/monocytes, eosinophils, and basophils.^{20,24,25} Interestingly, Sergejeva et al²⁶ have reported that during the pollen season, patients with sensitized allergic rhinitis showed increased numbers of CD34⁺ cells, CD34⁺/CXCR4⁺ cells, and CD34⁺ eosinophils into the nasal tissue suggesting that CXCL12/SDF-1 may also stimulate these cells to migrate at the allergic inflammatory site. The role of CXCL12/SDF-1 in angiogenesis and airways remodeling in asthma has been reported previously by Hoshino et al.¹⁵ In this study, they localized CXCL12/SDF-1 immunoreactivity in the subepithelial tissue including lymphocytes, macrophages, and endothelial cells. Consistent with their finding we have found

CXCL12/SDF-1 immunoreactivity localized to mononuclear cells in the subepithelial tissue and have extended these observations by demonstrating that the airway epithelium expresses increased CXCL12/SDF-1 immunoreactivity. Interestingly, in a murine model of airway epithelium injury, Gomperts et al²⁷ have shown increased CXCL12/SDF-1 in the tracheal epithelium, which further supports the involvement of these cells as cellular source of CXCL12/SDF-1.

Targeting the CXCL12/CXCR4 axis may constitute a novel target in asthma. This hypothesis is supported by studies conducted in murine models of asthma.^{13,14} Using a specific inhibitor of CXCR4, AMD3100, Lukacs et al¹⁴ demonstrated that blocking this receptor down-regulates the inflammatory process induced by allergen exposure, reduces airway hyperreactivity and peribronchial eosinophilia, and induces a shift in the cytokine profile. Indeed, AMD3100-treated sensitized mice showed a significant reduction in interleukin (IL)-4 and IL-5 levels and increased concentrations of IL-12 and interferon- γ in the lungs. Additionally, a number of novel CXCL12/SDF-1-neutralizing small molecules have also been found to be effective in preventing other lung diseases.²⁸

In summary, the present study has shown that patients with asthma release increased levels of CXCL12/SDF-1 in the airway epithelial lining fluid. Levels of this chemokine correlated with the number of several leukocytes including lymphocytes, macrophages, and eosinophils, suggesting that CXCL12/SDF-1 may contribute to their recruitment into the airways of patients with asthma. Thus, it is tempting to hypothesize that CXCL12/SDF-1 might provide a target for therapeutic intervention in asthma.

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Author contributions: Ms Negrete-García: contributed to design and experimental development.

Dr Velazquez: contributed to preparation, writing, and editing of the manuscript.

Dr Popoca-Coyotl: contributed to clinical study of the group of patients.

Ms Montes-Vizuet: contributed to analysis of results, preparation of graphs, and revision of the manuscript.

Ms Juárez-Carvajal: contributed to selection and processing samples.

Dr Teran: contributed to design and coordination of the project and writing the manuscript.

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REFERENCES

1. Holgate ST. Pathogenesis of asthma. *Clin Exp Allergy*. 2008;38(6):872-897.
2. Shirozu M, Nakano T, Inazawa J, et al. Structure and chromosomal localization of the human stromal cell-derived factor 1 (SDF1) gene. *Genomics*. 1995;28(3):495-500.

3. Gleichmann M, Gillen C, Czardybon M, et al. Cloning and characterization of SDF-1gamma, a novel SDF-1 chemokine transcript with developmentally regulated expression in the nervous system. *Eur J Neurosci*. 2000;12(6):1857-1866.
4. Yu L, Cecil J, Peng SB, et al. Identification and expression of novel isoforms of human stromal cell-derived factor 1. *Gene*. 2006;374:174-179.
5. Altenburg JD, Broxmeyer HE, Jin Q, Cooper S, Basu S, Alkhatib G. A naturally occurring splice variant of CXCL12/stromal cell-derived factor 1 is a potent human immunodeficiency virus type 1 inhibitor with weak chemotaxis and cell survival activities. *J Virol*. 2007;81(15):8140-8148.
6. McQuibban GA, Butler GS, Gong JH, et al. Matrix metalloproteinase activity inactivates the CXCL chemokine stromal cell-derived factor-1. *J Biol Chem*. 2001;276(47):43503-43508.
7. Atluri P, Woo YJ. Pro-angiogenic cytokines as cardiovascular therapeutics: assessing the potential. *BioDrugs*. 2008;22(4):209-222.
8. Chen M, Xie HQ, Deng L, et al. Stromal cell-derived factor-1 promotes bone marrow-derived cells differentiation to cardiomyocyte phenotypes in vitro. *Cell Prolif*. 2008;41(2):336-347.
9. Hernández-López C, Valencia J, Hidalgo L, et al. CXCL12/CXCR4 signaling promotes human thymic dendritic cell survival regulating the Bcl-2/Bax ratio. *Immunol Lett*. 2008;120(1-2):72-78.
10. Schönmeyer B, Kolodziej A, Schulz S, Jacobs S, Hoellt V, Stumm R. Regional and cellular localization of the CXCL12/SDF-1 chemokine receptor CXCR7 in the developing and adult rat brain. *J Comp Neurol*. 2008;510(2):207-220.
11. Zhang S, Qi L, Li M, et al. Chemokine CXCL12 and its receptor CXCR4 expression are associated with perineural invasion of prostate cancer. *J Exp Clin Cancer Res*. 2008;27:62-70.
12. Burns JM, Summers BC, Wang Y, et al. A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. *J Exp Med*. 2006;203(9):2201-2213.
13. Gonzalo JA, Lloyd CM, Peled A, Delaney T, Coyle AJ, Gutierrez-Ramos JC. Critical involvement of the chemotactic axis CXCR4/stromal cell-derived factor-1 alpha in the inflammatory component of allergic airway disease. *J Immunol*. 2000;165(1):499-508.
14. Lukacs NW, Berlin A, Schols D, Skerlj RT, Bridger GJ. AMD3100, a CXCR4 antagonist, attenuates allergic lung inflammation and airway hyperreactivity. *Am J Pathol*. 2002;160(4):1353-1360.
15. Hoshino M, Aoike N, Takahashi M, Nakamura Y, Nakagawa T. Increased immunoreactivity of stromal cell-derived factor-1 and angiogenesis in asthma. *Eur Respir J*. 2003;21(5):804-809.
16. Teran LM, Carroll MP, Frew AJ, et al. Leukocyte recruitment after local endobronchial allergen challenge in asthma. Relationship to procedure and to airway interleukin-8 release. *Am J Respir Crit Care Med*. 1996;154(2 pt 1):469-476.
17. Montes-Vizuet R, Vega-Miranda A, Valencia-Maqueda E, et al. CC chemokine ligand 1 is released into the airways of atopic asthmatics. *Eur Respir J*. 2006;28(1):59-67.
18. Busse WW, Wanner A, Adams K, et al. Investigative bronchoprovocation and bronchoscopy in airway diseases. *Am J Respir Crit Care Med*. 2005;172(7):807-816.
19. Synek M, Beasley R, Frew AJ, et al. Cellular infiltration of the airways in asthma of varying severity. *Am J Respir Crit Care Med*. 1996;154(1):224-230.
20. Bleul CC, Fuhlbrigge RC, Casasnovas JM, Aiuti A, Springer TA. A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1). *J Exp Med*. 1996;184(3):1101-1109.

21. Bleul CC, Farzan M, Choe H, et al. The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature*. 1996;382(6594):829-833.
22. Nagasawa T, Hirota S, Tachibana K, et al. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. *Nature*. 1996;382(6592):635-638.
23. Dorman SC, Babirad I, Post J, et al. Progenitor egress from the bone marrow after allergen challenge: role of stromal cell-derived factor 1alpha and eotaxin. *J Allergy Clin Immunol*. 2005;115(3):501-507.
24. Nagase H, Miyamasu M, Yamaguchi M, et al. Expression of CXCR4 in eosinophils: functional analyses and cytokine-mediated regulation. *J Immunol*. 2000;164(11):5935-5943.
25. Iikura M, Miyamasu M, Yamaguchi M, et al. Chemokine receptors in human basophils: inducible expression of functional CXCR4. *J Leukoc Biol*. 2001;70(1):113-120.
26. Sergejeva S, Malmhäll C, Lötvall J, Pullerits T. Increased number of CD34⁺ cells in nasal mucosa of allergic rhinitis patients: inhibition by a local corticosteroid. *Clin Exp Allergy*. 2005;35(1):34-38.
27. Gomperts BN, Belperio JA, Rao PN, et al. Circulating progenitor epithelial cells traffic via CXCR4/CXCL12 in response to airway injury. *J Immunol*. 2006;176(3):1916-1927.
28. Hogaboam CM, Carpenter KJ, Schuh JM, Proudfoot AA, Bridger G, Buckland KF. The therapeutic potential in targeting CCR5 and CXCR4 receptors in infectious and allergic pulmonary disease. *Pharmacol Ther*. 2005;107(3):314-328.

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