Age-Related Increased Prevalence of Asthma and Nasal Polyps in Chronic Rhinosinusitis and Its Association with Altered IL-6 Trans-Signaling

Seong H. Cho^{1,2,3*}, Dae Woo Kim^{2,4*}, Sun H. Lee¹, Narasaiah Kolliputi², Seung J. Hong³, Lydia Suh¹, James Norton¹, Kathryn E. Hulse¹, Sudarshan Seshadri¹, David B. Conley⁵, Robert C. Kern⁵, Bruce K. Tan⁵, Anju Peters¹, Leslie C. Grammer¹, and Robert P. Schleimer^{1,5}

¹Division of Allergy-Immunology, Department of Medicine, and ⁵Department of Otolaryngology, Northwestern Feinberg School of Medicine, Chicago, Illinois; ²Division of Allergy-Immunology, Department of Internal Medicine, University of South Florida College of Medicine, Tampa, Florida; ³Division of Rheumatology, Department of Medicine, Kyung Hee University School of Medicine, Seoul, Korea; and ⁴Department of Otorhinolaryngology-Head and Neck Surgery, Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea

Abstract

We report that S100 proteins were reduced in patients with chronic rhinosinusitis (CRS). S100A8/9, which is important in epithelial barrier function, was particularly decreased in elderly patients with CRS. Epithelial expression of S100A8/9 is partly regulated by the IL-6 trans-signaling pathway. The goal of this study was to investigate whether or not age-related reduction of S100A8/9 in CRS is associated with blunting of IL-6 trans-signaling. The levels of IL-6, soluble IL-6 receptor (sIL-6R), soluble gp130 (sgp130), and S100A8/9 from control subjects ($n = 10$), and patients with CRS without nasal polyps ($n = 13$) and those with CRS with nasal polyps (CRSwNP) ($n = 14$), were measured by ELISA. Age-related differences in the level of each protein were investigated. Normal human bronchial epithelial cells were cultured in air-liquid interface and stimulated with IL-6/sIL-6R and tumor necrosis factor (TNF)- α with or without the addition of sgp130, a natural inhibitor of IL-6 trans-signaling. There was a significant age-related decline in S100A8/9 and an increase in sgp130 in nasal tissue samples from patients with CRSwNP, although there was no age-related difference in IL-6/sIL-6R production.

Additionally, expression of the S100A8/9 gene and protein was increased significantly by IL-6/sIL-6R plus TNF- α in normal human bronchial epithelial cells. This increase was blocked by sgp130. These results suggest that increased sgp130 in older patients may inhibit IL-6 trans-signaling, impair barrier function, and decrease S100A8/9 production in elderly patients with CRSwNP. Restoration of barrier function by targeting sgp130 may be a novel treatment strategy.

Keywords: aging; chronic rhinosinusitis; nasal polyps; soluble gp130; S100A8/9

Clinical Relevance

Increased soluble gp130 in older patients may inhibit IL-6 trans-signaling, impair barrier function, and decrease S100A8/9 production in elderly patients with chronic rhinosinusitis with nasal polyps. Restoration of barrier function by targeting soluble gp130 may be a novel treatment strategy.

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*These authors contributed equally to this work.

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Correspondence and requests for reprints should be addressed to Seong H. Cho, M.D., Division of Allergy-Immunology, Department of Internal Medicine, 13000 Bruce B. Downs Boulevard (111D), Tampa, FL 33612. E-mail: scho2@health.usf.edu

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Studies of chronic rhinosinusitis (CRS) in the geriatric population are very limited. In a recent epidemiologic study of 4,098 subjects, the prevalence of CRS increased sharply between ages 50 and 59 years, then became twofold higher after ages 60 years and above (compared with young people between ages 19 and 39 years) (1). Using a large cohort study in the United States, we also showed that the incidence of CRS with nasal polyps (NP) (CRSwNP) between ages 65 and 74 years is twofold higher compared with CRS without NP (CRSsNP) or control subjects (2). To our knowledge, the inflammatory mechanisms of CRS in the elderly have not been well investigated despite their impact on health care for geriatric patients. Patients with CRS are often treated with extended courses of antibiotics and corticosteroids, and surgical intervention is recommended in medically unresponsive patients. During the clinical management of CRS, antibiotics remain widely prescribed, repeatedly or chronically, a practice that can result in the emergence of resistant, often deadly bacterial strains in the community. Commonly prescribed antibiotics to treat CRS, such as broad-spectrum penicillins/cephalosporins, fluoroquinolones, and clindamycin, can also cause *Clostridium difficile* colitis, which is more common and fatal in the elderly compared with younger adults (3). In fact, 90% of fatal *C. difficile* colitis cases are in individuals aged 65 years or older. The treatment of NP with antibiotics, steroids, and even surgery is often unsatisfactory, leading to a diagnosis of recalcitrant CRS and NP (4). This recalcitrant CRS and NP is further associated with severe and uncontrolled asthma, which is another health care issue of the elderly population (5).

CRSwNP also affects quality of life in elderly patients and age may be one of the risk factors for major complications of endoscopic sinus surgery (6, 7). Moreover, elderly patients with CRS usually have an age-related physiological impairment of olfaction and upper and lower respiratory function, often accompanied by other chronic illness, requiring additional therapies to be added to the numerous daily medications.

We recently reported that elderly patients with CRS had significantly higher computed tomography (CT) scores

compared with those of nonelderly patients (8). We also showed that the expression of S100 proteins is reduced in patients with CRS (9), and that S100A8/9 was further decreased in elderly patients with CRS (8). S100A8/9 is important in epithelial barrier function and has antimicrobial activity against bacteria and fungi (10). Epithelial expression of S100A8/9 is regulated by IL-6 and the signal transducer and activator of transcription 3 (STAT3) signaling pathway (11). Previously, we have reported reduced levels of phosphorylated STAT3 (pSTAT3) and increased soluble gp130 (sgp130), a natural inhibitor of IL-6 trans-signaling, suggestive of an altered IL-6 trans-signaling pathway in CRS (12, 13). We therefore hypothesized that the further reduction of S100A8/9 in elderly patients with CRS may reflect exaggerated blunting of IL-6 trans-signaling.

Materials and Methods

Subjects

In this study, a retrospective chart review of 390 patients with CRS who visited the allergy and otolaryngology clinics at Northwestern University between January 2008 and June 2011 was performed to investigate age-related differences in general clinical characteristics (Table 1). CRS diagnoses were based on personal medical history, physical examination, nasal endoscopy, and CT findings of the sinuses according to the European position paper on rhinosinusitis and nasal polyps (EPOS) 2012 guidelines (14). Among the 390 patients with CRS, we evaluated those who had consented to providing tissue samples during their sinus surgery and from whom we had banked nasal tissue samples available at the time of investigation. The control

specimens were derived from individuals without a history of CRS or asthma who underwent sinonasal surgery for unrelated reasons (e.g., skull base tumor). Details of the subjects' characteristics are displayed in Table 2. Patients who had taken oral or nasal steroids within 2 to 4 weeks prior to sample collection were excluded from this study. A description of patients as "elderly" was based on having attained an age of 60 years or more, as in our previous study (8). This study was approved by the institutional review board of Northwestern University.

ELISA

Extracts of sinonasal tissue or polyps were prepared by addition of 1 ml phosphate-buffered saline–Tween 20 at 4°C to fresh-frozen polyp/tissue samples. A cocktail of protease inhibitors purchased from Sigma Chemical Co. (St. Louis, MO) was added to the samples in a 1:100 dilution (10 μ L). The polyp/tissue samples were minced mechanically with a scalpel on ice and then homogenized for 30 to 60 seconds on ice with an IKA-WERKE Ultra-Turrax T8 Homogenizer (IKA Works Inc., Wilmington, NC). The suspensions were then centrifuged at 4,000 rpm for 20 minutes at 4°C. The tissue extracts were collected and stored at –80°C until use. Levels of IL-6 protein were determined by cytometric bead array assay (BD Biosciences, San Diego, CA). Levels of soluble IL-6 receptor (sIL-6R) and sgp130 were determined by ELISA (R&D Systems, Minneapolis, MN), and S100A8/9 were measured by ELISA (Hycult Biotech Inc., Plymouth Meeting, PA). The minimal detection limits for IL-6, sIL-6R, sgp130, and S100A8/9 assays were 20 pg/ml, 31.2 pg/ml, 0.125 ng/ml, and 1.6 ng/ml, respectively. All results were normalized to total protein concentration in the extracts

Table 1. Demographic and Clinical Characteristics of 390 Patients with Chronic Rhinosinusitis

	Nonelderly (n = 341)	Elderly (n = 49)	P Value*
Male/Female	180/161	29/20	NS
Age, median (range), y	39 (18–59)	67 (60–81)	
Nasal polyps, %	152 (44.6)	38 (77.6)	<.0001
Asthma, %	109 (32.0)	25 (51.0)	<0.01
Skin test, positive/performed (%)	148/180 (82.2)	15/19 (78.9)	NS

Definition of abbreviation: NS, not significant.

*P values are from the Chi-square test.

Table 2. Characteristics of Patients in Whom Immunologic Markers Were Measured

Immunologic Marker	Control Subjects	Patients with CRSsNP	Patients with CRSwNP
S100A8/9, <i>n</i>	10	13	14
Age, mean (range), y	40.8 (20-61)	42.0 (25-71)	51.8 (30-70)
Sex, M/F	4/6	5/8	8/6
Asthma	N/A	5	7
Inhaled steroids	N/A	1	2
Soluble gp130, <i>n</i>	9	13	13
Age, mean (range), y	56.4 (43-72)	36.9 (20-71)	49.6 (23-70)
Sex, M/F	3/6	4/9	12/1
Asthma	N/A	3	5
Inhaled steroids	N/A	1	2

Definition of abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; F, female; M, male; N/A, not applicable.

as determined by the Bio-Rad protein assay kit (Bio-Rad, Hercules, CA).

Cell Culture, Reagent, and Treatment

Normal human bronchial epithelial (NHBE) cells were cultured as described previously (15). Briefly, NHBE cells were obtained from Lonza (Walkersville, MD) and were maintained in serum-free bronchial epithelial cell growth medium (Lonza). Production of S100 proteins is differentiation dependent, and we used air-liquid interface (ALI) culture; NHBE cells were seeded onto transwells and grown to confluence in bronchial epithelial growth medium. Once confluent, medium from the upper chamber of the transwell was removed, initiating the transition to ALI culture conditions. NHBE cells were differentiated fully at Day 21 of ALI culture. Before stimulation, NHBE cells were cultured in bronchial epithelial cell growth medium without hydrocortisone for at least 2 days. NHBE cells were cultured with the following at the indicated concentration: 10 ng/ml tumor necrosis factor (TNF)- α (R&D Systems), 100 ng/ml IL-6 (Peprotech, Rocky Hill, NJ), 25 ng/ml IL-6R (Peprotech), and/or 250 ng/ml sgp130 (R&D Systems) for 48 hours.

Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Real-time reverse transcriptase–polymerase chain reaction was performed using the TaqMan method and a 7,500 Sequence Detection System (Applied Biosystems, Foster City, CA) in 20-ml reactions ($2 \times$ TaqMan Master mix [Applied Biosystems], with 400 nM of each primer,

and 200 nM TaqMan probe plus complementary DNA). Primer and probe sets for the following three genes were synthesized by Applied Biosystems: S100A8 (Hs00374264_g1), S100A9 (Hs00610058_m1), and β -actin (Hs01060665_g1). mRNA levels were expressed as relative gene copy numbers normalized to β -actin.

Statistical Analyses

All statistical analyses were performed with Prism GraphPad version 6, and ELISA data were analyzed using the Mann-Whitney *U* test. Correlations were assessed using the Spearman rank correlation. A *P* value of less than 0.05 was considered statistically significant.

Results

NP and Asthma Were More Prevalent in Elderly Patients with CRS

The patients with CRS were divided into nonelderly (18–59 y) and elderly (60–81 y) groups, and demographic and clinical characteristics were compared. In a previous study, we showed that CT scores were significantly higher in elderly patients with CRS compared with the nonelderly. Although there was a trend toward more prevalent NP and asthma in elderly patients with CRS compared with the nonelderly, it was not statistically significant (8). When 148 subjects were added to this analysis, NP and asthma were significantly more prevalent in elderly patients with CRS in our tertiary care cohort compared with nonelderly patients (Table 1).

Age-Related Decline in S100A8/9 in Patients with CRSwNP

We measured S100A8/9 protein levels in tissue extracts from normal control subjects, patients with CRSsNP, and patients with CRSwNP, and investigated the age-related differences. There was a significant age-related decline in S100A8/9 ($r = 0.705$, $P < 0.005$) (Figure 1A) and relatively lower levels of S100A8/9 in tissue extracts from elderly patients (62–70) with CRSwNP compared with nonelderly patients (30–55), although the *P* value was 0.0589, likely because of the small size of the elderly group (Figure 1B). This age-related decline was not observed in tissue extracts from patients with CRSsNP or normal control subjects (see Figure E1 in the online supplement).

sgp130 Levels Were Positively Correlated with Aging

S100A8/9 is known to be induced by IL-6 trans-signaling in epithelial cells. Therefore, we evaluated whether levels of IL-6, soluble IL-6R, pSTAT3, or sgp130 in nasal tissue extracts were correlated with age. We found that there was no correlation between levels of IL-6, sIL-6R, or pSTAT3 and age and no significant differences in the levels of IL-6, sIL-6R, or pSTAT3 between the elderly and nonelderly (Figures 2A and 2B) (pSTAT3 data not shown). However, sgp130 levels in nasal tissue samples from CRSwNP, but not from CRSsNP or normal control subjects, were significantly correlated with age and were higher in the elderly compared with the nonelderly (Figures 2C and 2D).

In Vitro Production of S100A8/9 Was Induced by IL-6 and Inhibited by sgp130 in Human Airway Epithelial Cells

Previous studies have shown that IL-6 induced the production of S100A8/9 from human skin epithelial cells (16). However, to our knowledge, there have been no published data as to whether the IL-6 signaling pathway is involved in the production of S100A8/9 in human airway epithelial cells. Therefore, we investigated whether or not human airway epithelial cells produce S100A8/9 via an IL-6 trans-signaling pathway. We first cultured NHBE cells using a submerged culture

Figure 1. Age-related differences in S100A8/9 in nasal tissue samples from patients with chronic rhinosinusitis with nasal polyps. (A) There was a significant negative correlation between S100A8/9 levels and age. (B) S100A8/9 levels in elderly patients were lower than those in nonelderly patients. The Mann-Whitney U test and the Spearman correlation test were used for between-group comparisons and variable correlation, respectively.

technique and stimulated them with IL-6/sIL-6R and TNF- α . Interestingly, there was no detectable level of secreted S100A8/9 in the culture media (data not shown). Therefore, we used an ALI culture technique because ALI culture cells are

fully differentiated and have tight junctions and cilia and it is generally considered that they more closely resemble airway epithelial cells *in vivo*. When we cultured ALI cells and stimulated the cells with IL-6/sIL-6R and TNF- α , we found

that gene expression of S100A8 and S100A9, as well as secreted protein of S100A8/9, in NHBE cells were significantly increased by IL-6/sIL-6R plus TNF- α (Figures 3A and 3B). (We also observed a modest increase with IL-6/sIL-6R or

Figure 2. Age-related differences of IL-6/soluble IL-6 receptor (sIL-6R) and soluble gp130 (sgp130) production in nasal tissue samples from patients with chronic rhinosinusitis with nasal polyps. (A and B) There was no significant correlation between IL-6/sIL-6R levels and age. (C) There was a significant positive correlation between sgp130 levels and age. (D) Levels of sgp130 in elderly patients were significantly higher than those in nonelderly patients. The Mann-Whitney U test and the Spearman correlation test were used for between-group comparisons and variable correlation, respectively.

Figure 3. Sgp130 inhibits the expression of S100A8/9 mRNA and protein in normal human bronchial epithelial cells. (A) S100A8 or S100A9 gene expression was normalized to β -actin and calculated as relative fold expression compared with medial control (1). S100A8 or S100A9 gene expression was increased with IL-6 (100 ng/ml)/sIL-6R (25 ng/ml) plus TNF- α (10 ng/ml) stimulation for 48 hours ($n = 3$). This gene induction was blocked by sgp130 (250 ng/ml) ($n = 3$). (B) S100A8/9 protein production was increased with IL-6 (100 ng/ml)/sIL-6R (25 ng/ml) plus TNF- α (10 ng/ml) stimulation for 48 hours. This increased production of S100A8/9 was blocked by sgp130 (250 ng/ml) ($n = 3$). The Mann-Whitney U test was then used for between-group comparisons. Data represent means $\pm$ SE of three independent experiments performed in duplicate.

TNF- α alone.) Furthermore, both the induced expression of S100A8 and S100A9 mRNA and the increased production of S100A8/9 protein were blocked by sgp130 (Figures 3A and 3B). These results indicate that IL-6 trans-signaling is active in stimulating S100A8/9 expression in human airway epithelial cells and that sgp130 acts as a significant inhibitor of IL-6 trans-signaling pathway in these cells.

Discussion

This study shows that, in our study population, the elderly patients with CRS had a higher prevalence of NP and asthma compared with the nonelderly. The treatment of NP with antibiotics, steroids, and even surgery is often unsatisfactory, leading to a diagnosis of recalcitrant CRSwNP. This recalcitrant CRSwNP is further associated with uncontrolled asthma, which is a serious health care issue in the elderly population, because older patients with asthma are more likely to be hospitalized than are younger patients with asthma and they have the highest death rate of any age group (17). Our study suggests that more careful investigation may be warranted in elderly patients with

uncontrolled asthma to determine whether undiagnosed CRSwNP contributes to treatment failure.

S100A8/9 plays an important role in epithelial barrier function by providing epithelial repair and antimicrobial activities (10). We reported previously that levels of S100A8/9 in nasal lavage samples from patients with CRS were inversely correlated with increasing age (8). In this study, we extended this finding of the age-associated reduction of S100A8/9 to include nasal tissue samples from patients with CRSwNP. We found that NP and asthma were significantly more prevalent in elderly patients with CRS; we further investigated the possible mechanism and found age-related elevations in levels of sgp130, with no difference in IL-6/sIL-6R levels in elderly patients with CRSwNP, suggesting an age-related blunting of the IL-6-S100A8/9 signaling pathway. IL-6 can activate gp130-positive cells that do not express IL-6R by binding to a sIL-6R that can form a complex with membrane-bound gp130 (18). This pathway has been termed “trans-signaling,” which enables IL-6 to regulate cells (e.g., epithelial cells) that would otherwise not respond to IL-6 because the cognate IL-6R is lacking. Soluble gp130 can act as a major negative

regulator of IL-6 trans-signaling and also inhibits the classical signaling pathway depending on the IL-6/sIL-6 ratio (19). Our findings suggest that the impairment of epithelial barrier function described by our laboratory and others may worsen with age and supports the hypothesis that one of the mechanisms of this impairment may be associated with elevated sgp130, causing blunted IL-6 trans-signaling and leading to reduced production of S100A8/9. These results could alter the microbiome or resistance to pathogens in elderly patients with CRSwNP and further enhance inflammatory responses. We demonstrate the blockade of IL-6-induced production of S100A8/9 by sgp130 in cultured human airway epithelial cells, suggesting that sgp130 is an important regulator of epithelial function and elevating its attractiveness as a potential therapeutic target in CRSwNP.

Conclusions

This study demonstrates that elderly patients with CRS in our study population have a higher prevalence of NP and asthma compared with the nonelderly patients. In addition, S100A8/9 was significantly

decreased in CRSwNP with aging, which may be because of alterations in the IL-6 trans-signaling pathway resulting from elevated sgp130 in the elderly. These results suggest that epithelial barrier

dysfunction may play a particularly important role in the pathogenesis of CRSwNP in the elderly, and restoration of barrier function, by targeting sgp130 or by other approaches, may be considered as

a treatment strategy for elderly patients with CRSwNP. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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