Up-regulation of the Mucosal Epidermal Growth Factor Receptor Gene in Chronic Rhinosinusitis and Nasal Polyposis

Guo Qiang Ding, MD; Chun Quan Zheng, MD; Shelly S. Bagga

Objectives: To investigate the expression of epidermal growth factor receptor (EGFR) messenger RNA (mRNA) in human sinus mucosa and to compare the expression of EGFR and EGF among patients with chronic rhinosinusitis (CRS), patients with CRS and nasal polyposis (CRS/NP), and a healthy control group.

Design: Maxillary sinus ostia mucosa was harvested from patients undergoing endoscopic sinus surgery for CRS or CRS/NP and from patients undergoing surgery for non-CRS pathologic conditions (control group). The samples were analyzed using semiquantitative reverse transcription–polymerase chain reaction to detect mRNA of EGFR. Hematoxylin-eosin staining and immunofluorescent staining were used to localize EGFR and EGF in the sinus mucosa.

Setting: Academic research.

Participants: Three groups (CRS, CRS/NP, and control), each with 10 subjects, were enrolled in the present study.

Main Outcome Measures: Area ratios of positive cells in the epithelia were compared among the CRS, CRS/NP, and control groups. In addition, eosinophils were counted in the subepithelial connective tissue in the 3 groups.

Results: The level of EGFR mRNAs in the sinus mucosa of the CRS and CRS/NP groups was statistically significantly increased compared with that in the control group (P < .01), and no statistically significant difference was found between the sinus mucosa of the CRS group and that of the CRS/NP group (P < .01). On hematoxylin-eosin staining, hyperplasia and metaplasia of epithelial goblet cells were present in the sinus mucosa of the CRS and CRS/NP groups. Epidermal growth factor receptor was mainly expressed in goblet cells and basal cells and was weakly expressed in ciliated cells, while EGF expression was located in epithelial cells and in some inflammatory cells but not in goblet cells. In the control group, expression of EGFR and EGF was lower compared with that in the CRS and CRS/NP groups. No statistically significant area ratios of positive cells differences in staining of EGFR and EGF were found between the CRS group and the CRS/NP group (P > .05), whereas statistically significant differences were found between the control group and the 2 CRS groups (P < .01). The number of eosinophils was statistically significantly increased in the CRS/NP group compared with that in the CRS group (P < .01).

Conclusion: Up-regulation of the EGFR cascade may have an important role regarding mucus production in the sinus mucosa of patients with CRS and CRS/NP associated with hyperplasia and metaplasia of epithelial goblet cells.


MUCUS SECRETION HAS A protective role in the normal human respiratory tract. However, in patients with chronic inflammatory airway diseases, excessive mucus secretions accumulate and can contribute to the pathogenesis of rhinitis, nasal polyps, acute asthma, cystic fibrosis, and chronic obstructive pulmonary disease. To date, no notably effective treatments for mucus hypersecretion have been found in these diseases.

Epidermal growth factor receptor (EGFR), as the prototype of the c-erbB receptor family, is a 170-kDa membrane glycoprotein that is activated by multiple ligands, including EGF, transforming growth factor α, heparin-binding EGF, and amphiregulin. The EGFR signaling pathway has been shown to be involved in different physiological cell responses, including proliferation, differentiation, motility, and survival. Many experiments primarily focused on the lower respiratory tract, have demonstrated that activation of
the EGFR signaling pathway can promote the secretion of mucins such as MUC5AC and MUC5B and that blockade of the EGFR cascade may provide potential treatment for mucus hypersecretion disease states.

Because most studies have focused on the expression of the EGFR gene in the lower respiratory tract, we know little about the expression of EGFR in disease states such as chronic rhinosinusitis (CRS) and CRS and nasal polyps (CRS/NP). The objective of this study was to explore the role of the EGFR cascade in the upper respiratory tract by evaluating patients with CRS and CRS/NP. We investigated the expression of EGFR messenger RNA (mRNA) in the sinus mucosa of healthy control subjects and in patients diagnosed as having CRS or CRS/NP using reverse transcription–polymerase chain reaction (RT-PCR), evaluated these samples using hematoxylin–eosin (HE) staining, and used immunofluorescent staining to localize EGFR and EGF. In addition, eosinophils were counted in the 3 groups to distinguish the differences related to the presence of a pathologic condition.

METHODS

SUBJECTS AND SAMPLE COLLECTION

Patients enrolled were previously diagnosed as having CRS or CRS/NP and were advised to undergo therapeutic functional endoscopic sinus surgery on the basis of their medical history, confirmed by computed tomography and nasal endoscopy. Each subject gave permission after informed consent using a protocol approved by the review board of Fudan University, Shanghai, China. Patients were separated into 2 study groups, a CRS group and a CRS/NP group, based on the presence or absence of polyposis after undergoing rigid nasal endoscopy or based on findings at the time of surgery. Each group comprised 10 subjects. Maxillary ostium mucosal samples were collected during surgery. A third control group comprised healthy maxillary ostium mucosal samples obtained from patients undergoing endoscopic sinus surgery for non-CRS pathologic conditions, including repairs for orbital wall blowout fracture, cerebrospinal fluid rhinorrhea, and proptosis of Grave disease.

Samples collected were divided into 3 portions. One portion for RT-PCR was immediately fresh frozen in liquid nitrogen and was stored at −80°C until used. The other 2 portions were fixed with 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS) (pH 7.4) and were stored overnight at 4°C for immunofluorescent staining and HE staining.

REVERSE TRANSCRIPTION–POLYMERASE CHAIN REACTION

Total RNAs from the sinus mucosal specimens were prepared using a commercially available kit (RNAeasy Mini Kit; Qiagen, Valencia, California) according to the manufacturer’s instructions. RNA was quantified by a spectrophotometer and was visualized by staining with ethidium bromide to determine RNA integrity. For all samples studied, absorbance ratios at 260/280 nm were between 1.8 and 2.0, and sharp 18S and 28S ribosomal RNA bands were present on the stained gel. Total RNA from each sample was reverse transcribed in 20 µL of reaction mixture containing 200 U of reverse transcriptase (Superscript II; Invitrogen Cor, CA) at 42°C for 50 minutes. Amplification of complementary DNA (cDNA) was performed using a commercially available product (2× Taq PCR MasterMix; Tian- gen Inc) in a thermocycler (iCycler; Bio-Rad Laboratories, Inc, Hercules, California). Primer for EGFR was designed using commercially available software (Primer Premier 5; Premier BioSoft International, Palo Alto, California) by inspection of the gene sequence; the forward primer was 5′-CAAGTCTCTGAGGAAGCCAACAAG-3′ and the reverse primer was 5′-CAGGTCATCTACCGAAGCCAAGGTCAAATACTCCCAG-3′. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal control for this study. The primers were 5′-GTGGAATTGTGCTAATTGACACG-3′ (forward) and 5′-GCCCTTCTGCTTTATGGTGATGAT-3′ (reverse). Amplification of cDNA was performed using 35 cycles at 94°C for 45 seconds, 60°C for 30 seconds of EGFR, 55°C for 30 seconds of GAPDH, and 72°C for 1 minute followed by a final extension cycle of 72°C for 7 minutes. After amplification, the PCR products were analyzed by electrophoresis on a 2% agarose gel and were visualized by ethidium bromide staining. The identity of each product was confirmed by molecular weight profile from the agarose gels. To verify that the amplified products were derived from mRNA but not from genomic DNA contamination, negative controls were designed by omitting the RT enzyme from some RT-PCR reactions. In the absence of RT enzyme, no PCR products were observed.

To analyze semiquantitatively the results of RT-PCR, we scanned the gel images and measured the intensity of the PCR product using commercially available software (Quantity One; Bio-Rad Laboratories, Inc). We determined the relative intensity of individual bands on a gel image as the ratio of the intensity of EGFR to the intensity of GAPDH. The negatives were scanned using a densitometer (GS-700TM Imaging; Bio-Rad Laboratories, Inc), and the signal was analyzed using commercially available software (ImageQuant; Amersham Biosciences, Piscataway, New Jersey).

HE STAINING AND IMMUNOFLUORESCENT STAINING

Hematoxylin–eosin staining and immunofluorescent staining were performed using optical cutting temperature medium–embedded sections. Samples were cut into 3-µm sections using a freezing microtome (CM3050S; Leica Microsystems, Nussloch, Germany). Hematoxylin–eosin staining was performed per standard protocols: cell nuclei were stained by hematoxylin, and cell plasma was stained by eosin. Results were observed using a light microscope (DMLS; Leica Microsystems). For immunofluorescent staining of EGFR and EGF, we used rabbit polyclonal antihuman EGFR and EGF antibodies (working dilution, 1:200; Santa Cruz Biotechnology, Inc, Santa Cruz, California). Hematoxylin–eosin staining and immunofluorescent staining were performed using reverse transcription–polymerase chain reaction (RT-PCR), evaluated these samples using hematoxylin–eosin (HE) staining, and used immunofluorescent staining to localize EGFR and EGF. In addition, eosinophils were counted in the 3 groups to distinguish the differences related to the presence of a pathologic condition.

According to the immunoreactivity, we analyzed area ratios of positive cells (ARPCs) in the epithelia. From each group, 10 samples of sections were randomly selected. Ten fields at high magnification (×200) were observed in each sample. Using ImageQuant software, we measured the whole area of epithelia and the area of positive cells in the epithelia and then calculated the ARPC in the epithelia and obtained the mean value.
and CRS/NP groups, the sinus mucosa showed strong expression of EGFR. The EGFR/GAPDH mRNA ratio in the sinus mucosa of the CRS and CRS/NP groups was statistically significantly increased compared with that in the control group \((P < .01)\), and no statistically significant difference in the ratio was found between the sinus mucosa of the CRS group and that of the CRS/NP group \((P > .05)\) (Figure 2). The PCR products extracted from the CRS and CRS/NP mucosa were 483 base pair (bp) for EGFR (Figure 1), which was expected given the selected primers. The internal control showed 271-bp bands for GAPDH not only in all the inflamed sinus mucosa but also in normal sinus mucosa. For the negative control RT-PCR, EGFR mRNA was not expressed.

LOCALIZATION OF EGFR AND EGF IMMUNOREACTIVITIES

On HE staining, the epithelium of normal sinus mucosa demonstrated a pseudostratified ciliated columnar epithelium with interspersed goblet cells, as well as non-ciliated and basal cells. As expected, an orderly ciliary arrangement was present with no inflammatory cell invasion. The epithelium in CRS and CRS/NP samples was different compared with that in the normal mucosa samples, demonstrating mucosal hypertrophy, hyperplasia, and metaplasia of epithelial goblet cells and submucosal glandular cells. Absence of partial cilia, as well as a large number of inflammatory cells such as plasma cells, lymphocytes, macrophages, and eosinophils, was noted in CRS and CRS/NP sinus mucosa (Figure 3). Furthermore, edema was found in submucosal tissue, especially in the submucosal glands of the CRS/NP group.

The level of expression of EGFR and EGF in different cell types was analyzed by immunofluorescent staining, the results of which are summarized in Table 1. Positively immunostained cells appeared green. In CRS and CRS/NP mucosa, EGFR immunoreactivity was abundant in the sinus epithelium (Figure 4). Moderate and strong EGFR immunoreactivity was found in goblet cells and basal...
cells, while weak immunoreactivity was found in ciliated cells and submucosal glandular cells. The ARPCs in the epithelia were 52.3%±4.6% and 56.3%±6.6% in the CRS group and the CRS/NP group, respectively. No statistically significant difference was found between these 2 groups (P<.05) (Table 2). In the control group, EGFR immunoreactivity was barely expressed (Figure 4), and the ARPC in the epithelia (5.9%±4.3%) was statistically significantly decreased compared with that of the CRS and CRS/NP groups (P<.01) (Table 2).

The EGF immunofluorescent analysis showed strong expression in the sinus epithelial cells of the CRS and CRS/NP samples (Figure 5), including ciliated and nonciliated epithelial cells. There was no positive staining in epithelial goblet cells, but some inflammatory cells were immunopositive to EGF. The ARPCs in the epithelia were 41.6%±10.8% and 43.8%±8.0% in the CRS group and the CRS/NP group, respectively. No statistically significant difference was found between these 2 groups (P>0.05) (Table 2). Weak to absent staining of EGF was found in the control group (Figure 5). The ARPC in the epithelia was 5.2%±4.5%, which is statistically significantly less than that of the CRS and CRS/NP groups (P<.01) (Table 2). No specific localization occurred in the negative controls, which confirmed the specificity of the EGFR and EGF antibodies.

### Table 1. Immunolocalization of Epidermal Growth Factor Receptor (EGFR) and EGF in Sinus Mucosa

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<th>Cell Type</th>
<th>Group</th>
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<th>−</th>
<th>+</th>
<th>++</th>
<th>+++</th>
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<th>P Value</th>
<th>χ²</th>
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<td>7/0</td>
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<td>0/1</td>
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<tr>
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<td>1/4</td>
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<td>7.1/5.2</td>
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<tr>
<td>CRS/NP</td>
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<td>1/4</td>
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<td>.008/ .02</td>
<td>0/0/0</td>
<td>&gt;.99/ &gt;.99</td>
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</tr>
</tbody>
</table>

Abbreviations: CRS, chronic rhinosinusitis; MH, Mantel-Haenszel χ² test; NP, nasal polyposis.

a − Indicates negative finding; +, weakly positive; ++, moderately positive; and ++++, strongly positive.
b Control group compared with the CRS group and the CRS/NP group, respectively.
c The CRS group compared with the CRS/NP group.

cells, while weak immunoreactivity was found in ciliated cells and submucosal glandular cells. The ARPCs in the epithelia were 52.3%±4.6% and 56.3%±6.6% in the CRS group and the CRS/NP group, respectively. No statistically significant difference was found between these 2 groups (P>0.05) (Table 2). In the control group, EGFR immunoreactivity was barely expressed (Figure 4), and the ARPC in the epithelia (3.9%±4.3%) was statistically significantly decreased compared with that of the CRS and CRS/NP groups (P<.01) (Table 2).

The EGF immunofluorescent analysis showed strong expression in the sinus epithelial cells of the CRS and CRS/NP samples (Figure 5), including ciliated and nonciliated epithelial cells. There was no positive staining in epithelial goblet cells, but some inflammatory cells were immunopositive to EGF. The ARPCs in the epithelia were 41.6%±10.8% and 43.8%±8.0% in the CRS group and the CRS/NP group, respectively. No statistically significant difference was found between these 2 groups (P>0.05) (Table 2). Weak to absent staining of EGF was found in the control group (Figure 5). The ARPC in the epithelia was 5.2%±4.5%, which is statistically significantly less than that of the CRS and CRS/NP groups (P<.01) (Table 2). No specific localization occurred in the negative controls, which confirmed the specificity of the EGFR and EGF antibodies.

### EOSINOPHIL COUNTING

The eosinophils in the subepithelial connective tissue were counted, and results showed that the numbers of eosin-
ophils were 1.46±0.60, 2.40±0.58, and 3.28±1.21 in the control group, the CRS group, and the CRS/NP group, respectively (Table 3). There were statistically significant differences among the 3 groups (P<.01), which confirmed that these 2 groups had pathologically distinct disorders.

In our study, RT-PCR demonstrated strong expression of EGFR mRNA in the sinus mucosa of patients with CRS and CRS/NP, whereas there was low expression of EGFR mRNA in the control subjects. Immunolocalization of EGFR using immunofluorescent staining demonstrated that the EGFR protein was primarily expressed in epithelial goblet cells and basal cells and was weakly expressed in ciliated sinus mucosal cells. No statistically significant difference was seen in the ARPCs of EGFR-stained epithelia between the CRS group and the CRS/NP group. However, statistically significant differences were found between the control group and the other 2 groups. Results of RT-PCR coincided with immunostaining data of EGFR, indicating that EGFR mRNA expression was consistent with EGFR expression in the sinus mucosa of these 3 groups.

Epithelial goblet cells are the main secretory cells in the airway tract, which can synthesize different mucins such as MUC5AC and MUC2.13-16 In our study, EGFR was strongly expressed in goblet cells, which confirms that the EGFR cascade is involved in the regulation of mucus production.9,10 In addition, the findings of hyperplasia and metaplasia of goblet cells in the mucosa of CRS and CRS/NP samples (demonstrated in the present study using HE staining) suggest an acceleration of mucus secretion. In a previous study,17 EGFR immunoreactivity was found in basal cells of bronchial epithelium using immunoelectron microscopy. We also observed a strong expression of EGFR in basal cells of the mucosa in patients with CRS and CRS/NP in this study. Therefore, our data for immunolocalization of EGFR in sinus epithelium are in accord with previously published data for bronchial tissue. Different findings were obtained by Burgel.
et al., who addressed the expression of EGFR in nasal polyps, which are not considerably different from the sinus-derived tissues investigated in the present study. There are 2 possible explanations for such differences. (1) Mucosa of the maxillary ostium, which locates at the center of the ostiomental complex, may have a more severe inflammatory reaction compared with that of polyp tissues. (2) A large number of inflammatory cells and EGFR ligands more easily activate the EGFR signal through ligand-dependent and ligand-independent pathways. Results similar to our findings were reported by Lee et al., who used the same tissue samples as ours.

In addition to EGFR, we studied the expression of its ligand, EGF, using immunofluorescent staining. Epidermal growth factor is synthesized as a transmembrane precursor protein in which the mature soluble growth factor sequence is located in the extracellular domain of the molecule. The membrane-bound precursor and the mature solubilized EGF are able to bind to the surface receptor (EGFR). Previous investigations have demonstrated EGF immunoreactivity in the glandular serous acini of rat and human nasal cavities. In human lung tissue, EGF was found in many inflammatory cells, including macrophages, eosinophils, and T lymphocytes. In the present study, in contrast to the expression of EGFR, EGF was not found in goblet cells but was found in CRS and CRS/NP sinus epithelial cells, as well as in some inflammatory cells. However, EGF was weakly expressed in the epithelial cells of normal sinus mucosa. We found similar results among the 3 groups when comparing the ARPCs of EGF and EGFR epithelia. These results demonstrate that EGFR and EGF are coexpressed in the sinus mucosa of patients with CRS and CRS/NP. No statistically significant difference between EGFR and EGF expression was found in the sinus mucosa of the CRS and CRS/NP groups. This indicates that EGFR and EGF may have a common role in the pathogenesis of CRS and CRS/NP.

The activation of EGFR signaling may involve 2 different pathways, ligand-dependent and ligand-independent EGFR tyrosine phosphorylation. In the present study, EGF, which was strongly expressed in the mucosa of the CRS and CRS/NP groups, may activate the EGFR signaling pathway by binding EGFR in the extracellular domain. In addition, activated neutrophils can initiate the EGFR signaling pathway by ligand-independent EGFR tyrosine phosphorylation via the production of oxidative stress and the release of oxygen free radicals. Other inflammatory cells such as macrophages and eosinophils recruited to the airway epithelium in inflammatory respiratory diseases express EGF ligands, suggesting that interactions between these cells and epithelial cells could result in ligand-dependent activation of EGFR signaling cascades. Therefore, we believe that the 2 pathways of EGFR activation participate in the pathogenesis of CRS and CRS/NP.

In summary, our study shows that EGFR is upregulated in the sinus mucosa of patients with CRS and CRS/NP, suggesting the potential role of the EGFR cascade for mucus production in nasal epithelium. Further study of the EGFR cascade is required to define its role in activation of nasal epithelium in response to inhaled

Table 3. Counted Numbers of Eosinophils in Subepithelial Connective Tissue

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mean ± SD</th>
</tr>
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<td>1.46 ± 0.60</td>
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<tr>
<td>CRS</td>
<td>10</td>
<td>2.40 ± 0.58</td>
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<td>CRS and nasal polyposis</td>
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<td>3.28 ± 1.21</td>
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Abbreviation: CRS, chronic rhinosinusitis.
irritants, toxins, infection, and inflammation, as well as potential treatment for mucus hypersecretion diseases by blocking the EGFR cascade.

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Author Contributions: Drs Ding and Zheng had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ding and Zheng. Acquisition of data: Ding and Zheng. Analysis and interpretation of data: Ding, Zheng, and Bagga. Drafting of the manuscript: Ding and Zheng. Critical revision of the manuscript for important intellectual content: Ding and Bagga.

Statistical analysis: Ding. Obtained funding: Bagga.

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REFERENCES


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