

Relation of epidermal growth factor receptor expression to goblet cell hyperplasia in nasal polyps

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Background: Because the epidermal growth factor receptor (EGFR) system regulates mucin production in airway epithelium, we hypothesized a role for this system in mucus hypersecretion that occurs in nasal polyposis.

Objective: We examined the relationship between goblet cell hyperplasia, EGFR expression, and inflammatory mediators produced by eosinophils and neutrophils in nasal polyp tissues.

Methods: Nasal polyp tissue samples from 8 patients and nasal turbinate biopsy specimens from 6 normal control subjects were examined for alcian blue/PAS staining, mucin MUC5AC (MUC5AC), and EGFR immunoreactivity and *EGFR* gene expression (in situ hybridization). We also examined the role of eosinophils and neutrophils in goblet cell hyperplasia.

Results: In control nasal mucosa alcian blue/periodic acid-Schiff- and MUC5AC-stained areas were $18.40\% \pm 1.31\%$ and $21.89\% \pm 1.43\%$, respectively. In polyps the alcian blue/periodic acid-Schiff- and MUC5AC-stained areas were $51.30\% \pm 5.85\%$ and $52.07\% \pm 6.58\%$, which was significantly larger than that found in control subjects (each comparison, $P < .01$). Four of 6 control specimens expressed EGFR messenger RNA and protein weakly in the epithelium. In polyps 4 of 8 specimens expressed *EGFR* gene and EGFR protein strongly; the EGFR-stained area was greater in hyperplastic than in pseudostratified epithelium. TNF- α immunoreactivity, expressed in eosinophils, was increased in EGFR-positive polyps compared with EGFR-negative polyps, suggesting a role for TNF- α in EGFR expression. Neutrophils were increased in the epithelium of EGFR-positive compared with EGFR-negative polyps, suggesting a role for these cells in mucin expression and in goblet cell degranulation. **Conclusion:** These data suggest a role for EGFR cascade in the regulation of goblet cell mucins in nasal polyps. Proof of concept will require clinical studies using selective EGFR inhibitors. (J Allergy Clin Immunol 2000;106:705-12.)

Key words: Airway epithelium, mucin MUC5AC, epidermal growth factor receptor, nasal polyps, neutrophils, eosinophils

Abbreviations used

AB/PAS: Alcian blue/periodic acid-Schiff
EGFR: Epidermal growth factor receptor
HNE: Human neutrophil elastase
TGF: Transforming growth factor

Nasal polyposis is a common chronic inflammatory disease of the upper airways affecting the well-being and quality of life of patients. Because the pathogenesis of the disease is poorly understood, medical and surgical therapy is not completely effective.¹ Common clinical features include nasal obstruction and rhinorrhea; the epithelium of nasal polyps frequently shows morphologic changes, including goblet cell hyperplasia.² Mucus hypersecretion is thought to contribute, at least in part, to these symptoms. Epithelial proliferation and differentiation have been implicated in the pathogenesis of nasal polyposis,³ but the underlying mechanisms are unknown. Polyps are reported to contain inflammatory cells,⁴ and these cells could play important roles in the disease.

Recently, a novel mechanism has been reported, which regulates mucin synthesis and goblet cell hyperplasia in human airway epithelial cells and the tracheal epithelium.⁵ Epidermal growth factor receptors (EGFRs), on activation by their ligands, induce the mucin *MUC5AC* gene and MUC5AC protein expression and goblet cell hyperplasia. In these in vivo and in vitro experiments, selective inhibitors of EGFR tyrosine phosphorylation were effective in preventing goblet cell growth, but EGFR inhibitors are not yet available for study in human subjects with inflammatory diseases. Therefore to examine the hypothesis that the EGFR system might be involved in mucus hypersecretion and mucus cell hyperplasia in human nasal polyps, we designed a study by using available morphologic information.

METHODS

Patients

Eight patients with nasal polyposis were included in the study. Nasal polyps were identified in patients on the basis of clinical symptoms (nasal obstruction, anosmia, sneezing, rhinorrhea, and itching), computed tomographic evaluation of the nasal fossae and paranasal sinuses, and visualization of polyps by means of anterior rhinoscopy. Patients with cystic fibrosis or primary ciliary dys-

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Stained Area of Epithelium

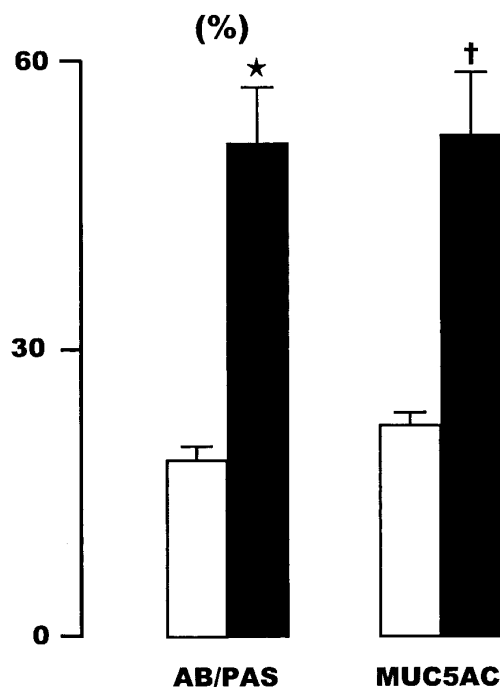


FIG 1. Percentage of AB/PAS- and MUC5AC-stained areas of epithelium in control (*open columns*) and nasal polyp (*filled columns*) epithelium. In control epithelium ($n = 6$) and in polyp epithelium ($n = 8$), AB/PAS- and MUC5AC-stained areas were not different from one another ($P > .05$). However, AB/PAS- and MUC5AC-stained areas were larger in polyp epithelium than in control epithelium (* $P = .002$ and † $P = .003$, respectively). Values are expressed as mean percentage areas $\pm$ SEM occupied by AB/PAS- and MUC5AC-stained cells.

kinesia were excluded from this study because of the special features of nasal polyps in these diseases. Subjects were requested to stop therapy for polyposis (ie, glucocorticoids and antibiotics) 1 month before surgery. Nasal polyps were removed in all patients at the beginning of the surgical procedure (endoscopic endonasal ethmoidectomy). At the time of surgery, none of the patients had evidence of local infection. As control subjects, 6 nonsmoking patients free of nasal symptoms and presenting a macroscopically normal mucosa on endoscopic examination were included in the study; nasal biopsy specimens were obtained from inferior turbinates removed during rhinoplasty. Nasal tissue samples were fixed immediately in formaldehyde and embedded in paraffin for morphologic studies. Neither patients nor control subjects had a clinical history or biologic evidence (Phadiatop test) of atopy. Informed consent was obtained from all patients, and permission was obtained from the Ethics Committee of Hôpital Henri Mondor (CCPPRB, Creteil, France).

Standard morphologic evaluation

Five-micrometer paraffin sections were obtained, deparaffinized, stained with Diff-Quik Stain Set (Baxter Healthcare Corporation, Miami, Fla) for morphologic studies, and stained with alcian blue/period acid-Schiff (AB/PAS) for mucous glycoconjugates.

Immunohistochemical localization of MUC5AC and EGFR in nasal specimens

Previously prepared 5- μ m paraffin sections were deparaffinized, rehydrated, and treated with 0.3% H_2O_2 in methyl alcohol. PBS containing 0.05% Tween-20 and 2% normal goat serum was used as diluent for the antibodies. Tissue sections were incubated with an mAb to EGFR (dilution, 1:200; Calbiochem, La Jolla, Calif) or an mAb to MUC5AC (dilution, 1:500; clone 45 M1; Neomarkers, Fremont, Calif) at room temperature for 2 hours. Sections were then incubated with biotinylated horse anti-mouse antibody (dilution, 1:250; Vector laboratories, Burlingame, Calif) at room temperature for 1 hour. Bound antibody was visualized according to standard protocols for the avidin-biotin-peroxidase complex method (Elite ABC kit, Vector laboratories). Tissue sections were counterstained with hematoxylin stain. Tissue preparations of polyps and control nasal mucosa were performed concomitantly. Omission of the primary antibody was used as negative control.

Quantification of AB/PAS-, MUC5AC-, and EGFR-stained areas

Quantification of AB/PAS staining and of MUC5AC and EGFR immunoreactivity was assessed by using a semiautomatic imaging system.⁶ Sections were counted by a single blinded observer on two separate occasions in coded random order, as described previously.⁷ Images of the epithelium of nasal specimens were recorded from 10 high-power fields with a phase-contrast lens at 400 $\times$. We measured AB/PAS-, MUC5AC-, and EGFR-stained areas and the total epithelial area, and we expressed the data as the percentage of total area stained by AB/PAS, stained by an antibody to MUC5AC, or stained by an antibody to EGFR. Analyses were performed with the public domain National Institutes of Health IMAGE program.⁶

First, we examined the percentage of stained areas for AB/PAS and MUC5AC, comparing control and polyp epithelium. In control specimens the epithelium was uniformly pseudostratified, and therefore sampling was straightforward. However, as described previously,⁸ the surface epithelium of nasal polyps presented varying morphologic subtypes: (1) normal pseudostratified epithelium (composed of ciliated cells, goblet cells, and a single layer of basal cells); (2) hyperplastic epithelium consisting of ciliated cells and basal and goblet cells (containing more than 3 cell layers, either basal cells, mucous cells, or both); and (3) epithelial damage. Squamous metaplasia was not observed in our specimens. For sampling, we had to consider this heterogeneity. First, the stained slides were examined under low magnification. Areas of epithelial damage (exfoliated surface epithelia) were excluded from the analysis. We determined the areas of pseudostratified and hyperplastic epithelium in each polyp. Similar to previous studies,⁸ large differences existed among the different specimens. Pseudostratified epithelium occupied a mean of 25% (range, 14%-56%), and hyperplastic epithelium occupied a mean of 75% (range, 44%-100%) of the intact polyp epithelium. To examine the percentage of areas stained in polyps, we obtained images of representative areas (10 high-power fields) randomly in proportion to the percentage of pseudostratified and hyperplastic epithelium in each polyp.

Because we found that goblet cells were more concentrated in areas of hyperplastic than pseudostratified epithelium, we compared the EGFR protein expression in the two areas. In these studies images of 10 high-power fields of the two types of epithelium stained for MUC5AC protein were obtained randomly and compared with the same areas of adjacent sections stained for EGFR protein.

Because only half of the polyp specimens expressed EGFR, we determined the relationship between EGFR and MUC5AC staining in the polyps, examining 10 high-power fields of adjacent stained specimens.

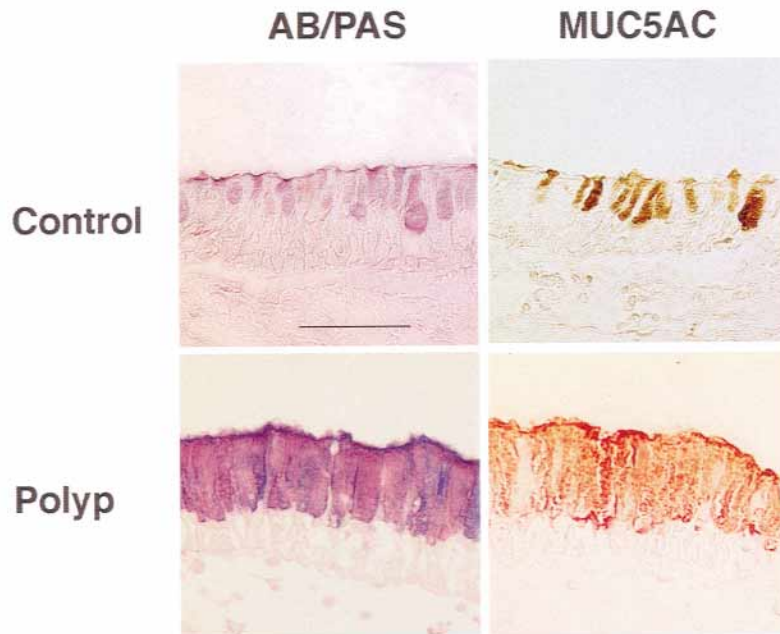


FIG 2. Comparison of AB/PAS staining (*left panels*) and MUC5AC protein immunolocalization (*right panels*) in control and polyp nasal epithelium. In control nasal epithelium (*upper panels*), staining with AB/PAS (for mucous glycoconjugates: *left panel*) and staining for mucin MUC5AC protein (*right panel*) was positive in only a few goblet cells. In polyp epithelium (*lower panels*) AB/PAS and MUC5AC staining was also positive in goblet cells; the stained areas were larger than in control epithelium (*bar* = 50 μ m).

The within-observer coefficient of variation for repeated measurements of immunoreactive areas was less than 9%.

EGFR and MUC5AC gene expression in nasal tissue

EGFR gene expression was assessed by in situ hybridization with ^{35} S-labeled riboprobes. A 350-bp fragment was isolated from pTRI-EGFR human template (Ambion, Austin, Tex) and subcloned into the *Kpn*I and *Eco*RI sites of Bluescript II SK-vector (Stratagene, La Jolla, Calif). For MUC5AC, riboprobes were generated from plasmids containing human MUC5AC; probe isolation and in situ hybridization were performed as described previously.⁶

Immunohistochemical localization of TNF- α in nasal polyps

Sections were stained with a polyclonal rabbit anti-human antibody to TNF- α (dilution, 1:1000; Genzyme Corp, Cambridge, Mass). Quantification was performed by examining 10 consecutive high-power fields (400 $\times$), 5 in the subepithelial area and 5 in the stromal area, as described previously.⁹ The values reported are expressed as positive cells per 0.25 mm² (one high-power field).

Immunohistochemical staining for neutrophils

We used two antibodies to identify neutrophils in the tissue specimens: (1) a mouse mAb to human neutrophil elastase (HNE; dilution, 1:5000; DAKO Corp, Carpinteria, Calif) and (2) an mAb to CD16 (dilution, 1:500; BioSource International, Camarillo, Calif), which binds to the low affinity Fc receptor (Fc γ RIII) present on the neutrophil cell surface and which has been shown previously to distinguish neu-

trophils (CD16⁺) from eosinophils (CD16⁻).¹⁰ For the staining technique, see the section describing MUC5AC and EGFR staining.

Recruited neutrophils were assessed by counting HNE- and CD16-stained cells in the epithelium of nasal polyps. For each specimen, images of 10 consecutive high-power fields (400 $\times$) were obtained, and the positively stained cells were counted. Results are expressed as the number of positively stained cells per 0.25 mm of basal lamina (one high-power field).

Statistical analysis

Data obtained from measurements of AB/PAS-, MUC5AC-, EGFR-, TNF- α -, HNE- and CD16-stained cells were compared by using the nonparametric Mann-Whitney *U* test. A *P* value of less than .05 for the null hypothesis was accepted as indicating a statistically significant difference.

RESULTS

Mucous glycoconjugates and mucin MUC5AC in normal and polyp nasal epithelium

In both normal and polyp nasal epithelium, AB/PAS and MUC5AC staining was positive. The areas of epithelium occupied by AB/PAS and MUC5AC staining were not different from one another either in the control subjects or in the subjects with polyps (*P* = .91 and *P* = .10, respectively; Fig 1). However, the mean percentage of stained areas was significantly larger in polyps than in control epithelium (each comparison, *P* < .01). In Fig 2 representative sections are shown.

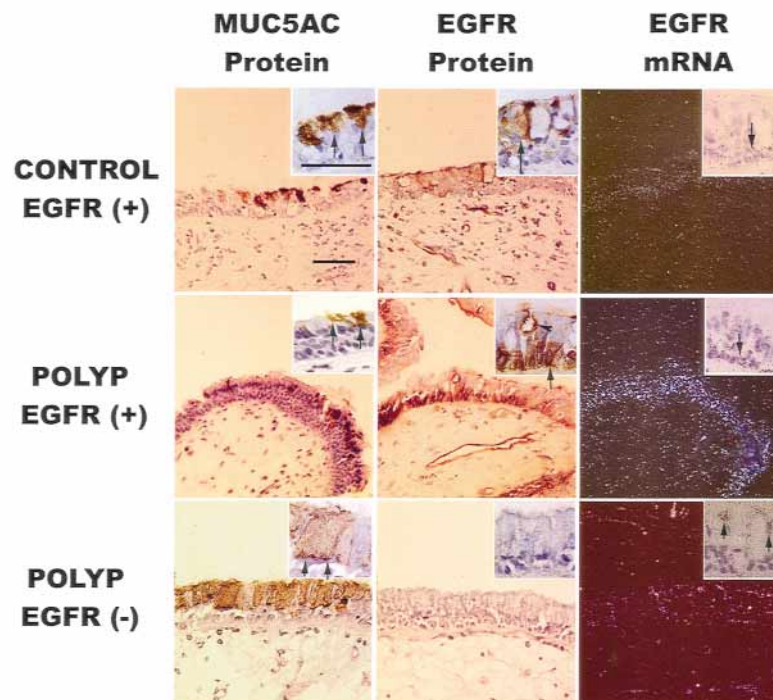


FIG 3. Comparison of MUC5AC protein immunolocalization (*left panels*), EGFR protein immunolocalization (*middle panels*), and in situ hybridization for EGFR messenger RNA (*right panels*) in control nasal tissue (*upper panels*) and in two types of nasal polyps (EGFR-positive and EGFR-negative, *middle and lower panels*). In the epithelium of EGFR-positive control subjects (*upper panels*), the MUC5AC antibody stained few goblet cells (*insert, arrows*). *EGFR* gene and EGFR protein expression was weak; no EGFR expression was seen in the basal epithelium. In the epithelium of EGFR-positive polyps (*middle panels*), MUC5AC staining was greater than in control epithelium. Some goblet cells were seen secreting (*insert, arrows*), suggesting active goblet cell degranulation. *EGFR* gene and EGFR protein expression was strong and concentrated in the basal epithelium. In the epithelium of EGFR-unstained polyps (*lower panels*), the MUC5AC-stained goblet cell area was larger than in EGFR-positive polyps and extended throughout the elongated cells (*arrows*). EGFR in situ hybridization showed little expression (*insert, arrows; bar = 50 μ m; original picture magnification, 200 $\times$; inserts, same area, 1000 $\times$*).

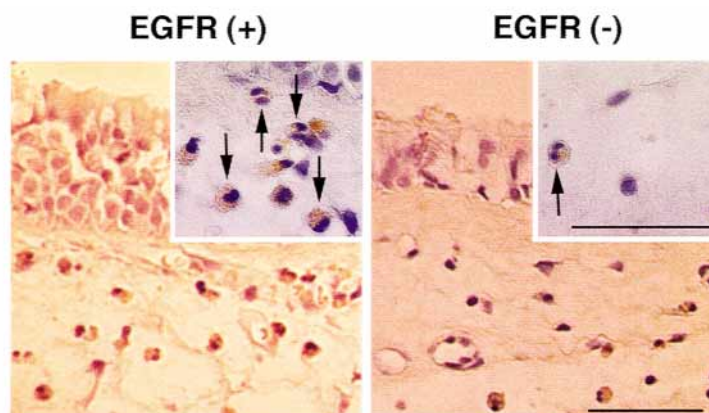


FIG 4. TNF- α immunolocalization in nasal polyps. After staining with a polyclonal antibody to TNF- α , both EGFR-positive and EGFR-negative tissues showed immunoreactivity in stromal inflammatory cells. However, EGFR-positive polyps contained more cells expressing TNF- α immunoreactivity than EGFR-negative polyps ($P = .02$). Among the cells that showed immunoreactivity, eosinophils (*arrows*) with characteristic bilobed nuclei were the most common cells (*bar, 50 μ m; original picture magnification, 200 $\times$; inserts, 1000 $\times$*).

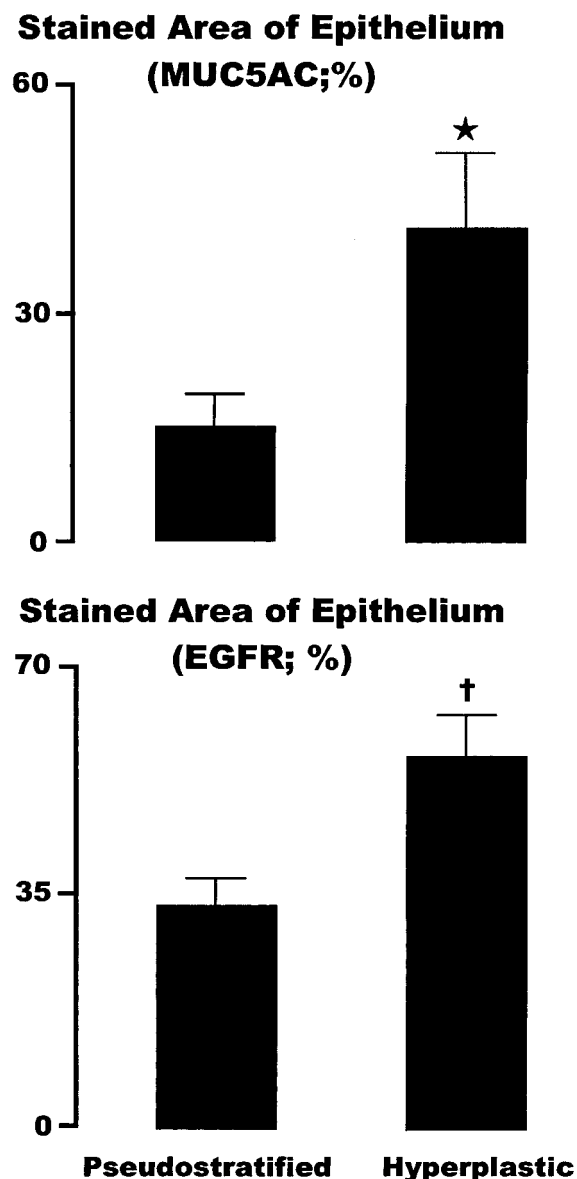


FIG 5. Comparison of MUC5AC- and EGFR-stained areas in pseudostratified and hyperplastic epithelium in polyps. In EGFR-stained polyps ($n = 4$) hyperplastic epithelium contained a greater area of MUC5AC-stained cells (*upper columns*, $*P < .05$) and a greater area of EGFR-stained cells (*lower columns*, $\dagger P < .05$) than in pseudostratified epithelium. Results are expressed as mean percentage stained areas $\pm$ SEM.

EGFR gene and EGFR protein expression in nasal epithelium

In the control specimens there was little or no *EGFR* gene or EGFR protein expression: two of the 6 specimens had no *EGFR* gene or EGFR protein (data not shown). The 4 other specimens showed little *EGFR* gene expression (Fig 3, *upper panel, right, arrow*); only weak EGFR immunoreactivity was present in goblet cells and in nongranulated secretory cells (Fig 3, *upper panel, middle, arrow*). No immunoreactivity was seen in basal or ciliated cells.

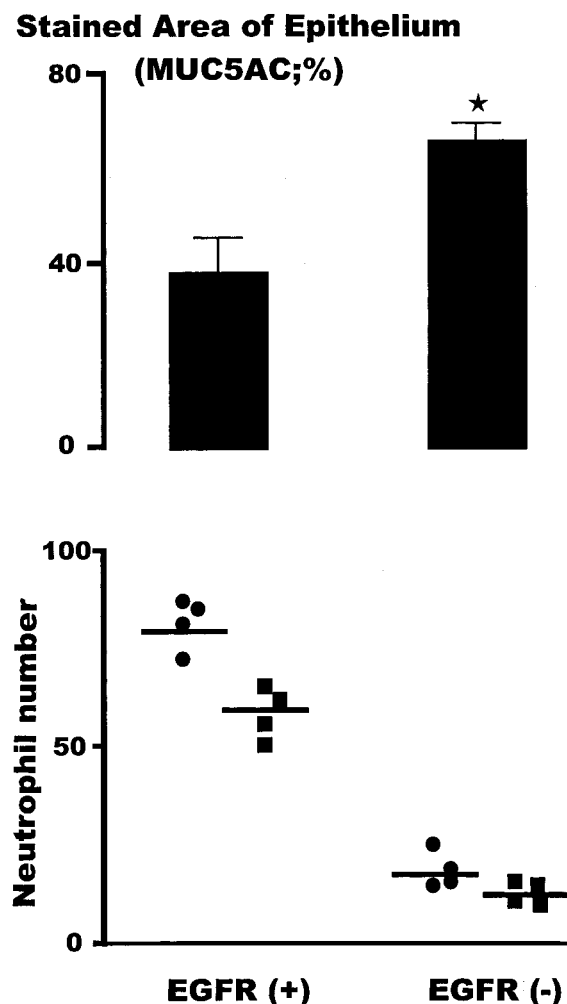


FIG 6. Percentage of MUC5AC-stained area of epithelium (*upper*) and neutrophil infiltration (*lower*) in EGFR-positive (*left*) and EGFR-unstained (*right*) polyps. Surprisingly, the EGFR-unstained polyps contained greater areas of epithelial MUC5AC staining (*upper panel, right*) than polyps with EGFR staining (*upper panel, left*, $*P < .05$). Neutrophils (*lower panel*) assessed by elastase-stained (filled circles) and CD16-stained (filled squares) cells were more concentrated in the epithelium of EGFR-positive polyps ($n = 4$) than in the epithelium of EGFR-unstained polyps ($n = 4$, $P < .05$). Data are reported as the number of positive cells per 0.25 mm of basal lamina.

Two types of polyps were found. Four of 8 specimens had strong *EGFR* gene (Fig 3, *middle panel, right*) and EGFR protein (Fig 3, *middle panel, middle*) expression. In these specimens intense EGFR immunoreactivity was localized in basal cells (Fig 3, *arrow*); some nongranulated secretory and goblet cells were stained (Fig 3, *arrowhead*). Ciliated cells were unstained. The mean percentage area of EGFR-positive staining in these polyps was greater than in the epithelium of the 4 control subjects who had EGFR staining ($44.07\% \pm 5.95\%$ vs $19.55\% \pm 1.44\%$, $P = .02$).

The 4 remaining polyps showed no *EGFR* gene (Fig 3, *lower panel, right*) or EGFR protein (Fig 3, *lower panel, middle*) expression.

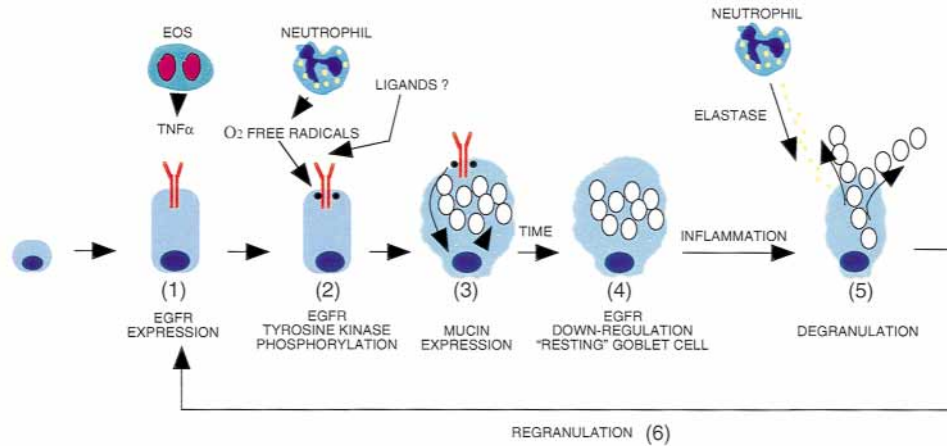


FIG 7. Hypothetical mechanism for goblet cell production in nasal polyps. 1, Eosinophils (EOS), on recruitment and activation, release TNF- α , which induces EGFR expression in epithelial basal cells. 2, Neutrophils, on recruitment and activation, cause EGFR tyrosine kinase phosphorylation (eg, transphosphorylation by oxygen-free radicals). EGFR activation may also occur by the release of EGFR ligands (autophosphorylation) by various cells. 3, Activation of the EGFR cascade results in mucin synthesis and storage. 4, When the inflammatory process resolves, EGFR downregulation occurs. The goblet cells become quiescent (resting cells). 5, Subsequent inflammation induces the recruitment of inflammatory cells to the epithelium. Activated neutrophils may release elastase, which causes goblet cell degranulation. 6, After neutrophil-induced goblet cell degranulation, regranulation may occur through the same mechanism.

TNF- α immunolocalization in nasal specimens

In control specimens there was no TNF- α immunoreactivity (not shown). In polyps TNF- α staining was present and concentrated in inflammatory cells in the subepithelial layer and in the deep stromal layer. Most of these cells were eosinophils with a characteristic bilobed nucleus (Fig 4), but some mononuclear cells and neutrophils also stained positively. The EGFR positively stained polyps contained more TNF- α -stained cells than the EGFR-unstained polyps (19.55 ± 1.13 vs 9.02 ± 0.41 cells/0.25 mm², $P = .02$, $n = 4$).

Relationship of EGFR expression to mucin MUC5AC

Comparison of pseudostratified and hyperplastic epithelium in polyps. The surface epithelium of polyps was composed of pseudostratified and hyperplastic epithelium (see the "Methods" section). Because we found that the areas of hyperplastic epithelium contained a significantly greater percentage epithelial area with AB/PAS- and MUC5AC-positive staining than the pseudostratified areas (not shown), we hypothesized that EGFR might be more strongly expressed in the areas of hyperplastic epithelium than in the areas of pseudostratified epithelium. We found that in the epithelium of EGFR-positive polyps, hyperplastic epithelium, which contained a greater area of MUC5AC staining (Fig 5, upper columns), also contained a greater area of EGFR-positive staining than pseudostratified epithelium (Fig 5, lower columns).

Relationship between EGFR positivity and mucin

MUC5AC gene and protein expression in polyps. Because EGFR activation has been shown to cause mucin expression in the airway epithelium, we examined the relationship between EGFR positivity and mucin expression in the epithelium. First, these studies showed that specimens that expressed EGFR also showed mucin MUC5AC gene expression (not shown). Next, we examined the relationship between EGFR positivity in the epithelium and MUC5AC protein staining. Surprisingly, the EGFR-stained group had a lower MUC5AC-stained area than the group of polyps that did not have EGFR immunoreactivity (Fig 6, upper panel). However, in the EGFR positively stained polyps, goblet cells were smaller and there were large MUC5AC-stained areas in the lumen, providing morphologic evidence of mucin discharge into the lumen, whereas in the polyps that showed no EGFR immunoreactivity, goblet cells appeared to be larger and showed minimal evidence of MUC5AC staining in the lumen.

Neutrophil infiltration in polyp epithelium

Because activated neutrophils have been implicated in goblet cell degranulation and mucin production, we examined intraepithelial neutrophils in polyp specimens. We found that the number of neutrophils in the epithelium was increased in EGFR-positive specimens compared with EGFR-unstained specimens (Fig 6, lower panel).

DISCUSSION

We hypothesize that the goblet cell hyperplasia observed in nasal polyposis^{11,12} is due to a cascade

involving EGFR activation. First, we confirmed that goblet cell hyperplasia occurs in polyps and that mucin MUC5AC is expressed in both nasal polyp and normal nasal epithelium. These findings are in agreement with the reports that show the presence of MUC5AC messenger RNA found in nasal polyp tissue¹³ and in normal nasal mucosa from the inferior turbinate.¹⁴ Examining EGFR expression, we show, for the first time, *EGFR* gene and EGFR protein expression in human nasal polyps and normal nasal epithelium.

Next, we examined the relationship between EGFR expression and goblet cell mucin production. In EGFR-positive specimens, EGFR was expressed to a much greater extent in polyp epithelium (which contained a large amount of mucin) compared with control epithelium (which contained a smaller amount of mucin). In EGFR-positive polyps the hyperplastic epithelium contained a much greater area of EGFR and goblet cells than the pseudostratified epithelium. These results are compatible with the hypothesis that EGFR expression is a prerequisite to mucin production.

The proinflammatory cytokine TNF- α has been shown to induce EGFR expression in various epithelial cell lines^{5,15} and in rat airway epithelium *in vivo*.⁵ In the present study polyps positively stained for EGFR contained more cells staining for TNF- α than EGFR-unstained polyps, suggesting that TNF- α may be responsible for EGFR expression in nasal polyp epithelium. Because eosinophils are the most prominent cell type in the cellular infiltrate of nasal polyps,¹⁶ and because we found that TNF- α is highly expressed in eosinophils of polyps (confirming a previous report⁹), these cells are likely to be the major source of TNF- α in nasal polyps. However, other cells, such as neutrophils¹⁷ and macrophages,¹⁸ that produce TNF- α could also contribute.

When EGFR is present in the epithelium, receptor activation can occur by binding of an EGFR ligand, such as transforming growth factor α or epidermal growth factor (ligand-dependent autophosphorylation).¹⁹ This activation results in mucin gene and protein production.⁵ In nasal polyps eosinophils are a major source of EGFR ligands because the *TGF- α* gene and transforming growth factor α protein are mainly expressed in eosinophils.²⁰ In addition, EGFR activation may occur through ligand-independent transactivation.²¹ Neutrophils were more concentrated in the epithelium of EGFR-positive polyps than in the epithelium of EGFR-unstained polyps. Activated neutrophils release free radicals,^{22,23} which are capable of promoting EGFR activation through a ligand-independent process.²⁴⁻²⁶ In addition, neutrophil recruitment into the respiratory epithelium causes goblet cell degranulation through the release of neutrophil elastase.²⁷ Thus activated neutrophils recruited into polyp epithelium could be involved in goblet cell production and degranulation.

The present understanding of the relationship between the cells that express EGFR and goblet cell growth derives from studies of bronchi in rats⁵: The lower airways of pathogen-free rats do not contain EGFR,²⁸ but stimulation with TNF- α causes the expression of EGFR.

Staining first occurs on the luminal surface of basal cells; over 24 to 48 hours, the cells elongate and stain positively for EGFR protein (J.A. Nadel, unpublished data). Subsequent EGFR activation causes progressive staining for mucous glycoconjugates, and the cells become *pregoblet* and then goblet cells. In the present study 4 of the polyps showed a pattern compatible with this sequence: they had intense EGFR expression in the basal area of the epithelium and mucin staining in goblet cells. The 4 remaining polyps showed little or no *EGFR* gene or EGFR protein expression in spite of the fact that they contained large areas of mucin-containing cells. There are several possible explanations for the absence of EGFR expression in some polyps: (1) mucin production in these polyps could be independent of the EGFR cascade, and (2) downregulation of EGFR could occur when goblet cells fill with mucins but when goblet cell degranulation does not occur. Studies of nasal epithelium in pathogen-free rats are relevant here.²⁹ In the control state approximately 20% of the nasal epithelial area was occupied by AB/PAS- and MUC5AC-stained epithelium. Morphologic studies showed no evidence of goblet cell degranulation, and EGFR expression was absent. However, after neutrophil-dependent goblet cell degranulation,²⁷ EGFR expression was intense and was associated with regranulation and neutrophil influx. Pretreatment with an EGFR tyrosine kinase inhibitor completely prevented regranulation. Thus inactive goblet cells do not appear to be associated with EGFR expression, but neutrophil-dependent degranulation is followed by upregulation and activation of EGFR, resulting in mucin production. On the basis of these findings, we present a hypothesis for goblet cell growth in nasal polyps involving an EGFR cascade, which is illustrated in Fig 7. When EGFR inhibitors are available clinically for use in inflammatory diseases, definitive studies defining the role of EGFR activation in polyp growth and in mucus differentiation can be better defined.

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