Remodeling in Chronic Sinusitis and Nasal Polyps
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ABSTRACT
Remodeling in chronic sinusitis and nasal polyps is discussed. In chronic sinusitis, epithelial shedding, which is characteristic of asthma, is not observed in the maxillary sinus. An increase of microvillous cells, squamous metaplasia, and goblet cells is observed in many patients with chronic sinusitis. The decreased ciliary area increases postoperatively in the maxillary ostium and in the maxillary sinus. There is no significant difference in the number of goblet cells between normal controls and chronic sinusitis. On the other hand, the number of submucosal acinar cells in chronic sinusitis is significantly higher than that in normal controls. Nasal polyps show a diversity of histological findings. Although squamous metaplasia and goblet cells hypertrophy is observed in many patients, epithelial shedding, which is characteristic of asthma, is not observed in nasal polyps. The most striking finding of glands in nasal polyps is long shape. Histochemical analysis reveals deposition of types I, III, and V collagens in nasal polyps. Myofibroblasts, which are abundant in nasal polyps but rare in nasal mucosa, could be involved in the growth process of nasal polyps by inducing extracellular matrix accumulation. Although accumulation of extracellular matrix is a main feature of nasal polyps, its pathogenesis is not clearly known.

KEY WORDS
airway remodeling, asthma, chronic sinusitis, extracellular matrix, nasal polyps

INTRODUCTION
Not much attention has been paid to the remodeling process of chronic sinusitis and nasal polyps. Here we will discuss remodeling of chronic sinusitis and nasal polyps. Historically, sinusitis was divided into three categories based on disease duration, with chronic sinusitis referring to patients whose symptoms were of greater than 6 weeks’ duration. At the time this terminology was developed, all sinusitis was thought to be infectious. It is now clear, however, that the majority of patients with chronic sinusitis do not have an infectious disorder, and this has led to the need to develop more appropriate terminology to describe the myriad of conditions that make up chronic sinusitis. There are 4 major pathophysiologic processes responsible for chronic sinusitis. Only a small subset of patients in fact have chronic infectious sinusitis. These patients typically have underlying humoral immune deficiencies, HIV, Kartagener syndrome, and cystic fibrosis. In contrast, most patients with chronic sinusitis have an inflammatory disorder with prominent hyperplasia of immune cells. Chronic inflammatory sinusitis is thought to result from chronic or recurrent occlusion of the sinus ostia caused by viral rhinitis, allergic rhinitis, anatomic predisposition, or other causes. These processes lead to recurrent acute bacterial infections, possibly in association with barotrauma of the sinus cavities and damage to the respiratory epithelium, ciliary destruction, mucous gland and goblet cell hyperplasia, bacterial colonization, and ultimately, chronic inflammatory changes. Eosinophils are not a feature of chronic inflammatory sinusitis, although this disorder might produce nasal polyps. Chronic inflammatory sinusitis is generally responsive to surgical interventions. In contrast to chronic inflammatory sinusitis, the other immune inflammatory disease is characterized by prominent expression of eosinophils and perhaps should be referred to as chronic hyperplastic eosinophilic sinusitis. This disease is frequently associated not only with nasal polyps but also with asthma, atopy, aspirin sensi-
CHRONIC SINUSITIS

EPITHELIAL ABNORMALITIES

The normal nasal and paranasal epithelium is a stratified structure consisting of a columnar layer comprising ciliated and secretory cells supported by basal cells. In the normal maxillary sinus, more than 90% of the mucosal surface area is covered with cilia. In order to quantitate epithelial abnormalities in chronic sinusitis, the maxillary mucosa of both the superolateral wall and the ostium were sampled during endonasal sinus surgery. Ciliary surface was determined using scanning electron microscopy and was expressed in terms of ciliary area, which is the percentage of mucosal surface occupied by cilia. The mean ciliary area at the time of surgery was 61% and 40% in the superolateral wall of the maxillary sinus and the ostium of the maxillary sinus, respectively.

Although the increase of mirovillous cells, squamous metaplasia, and goblet cells was observed in many patients, epithelial shedding, which is characteristic of asthma, was not observed in the maxillary sinus. In the inferior turbinate mucosa, epithelial shedding was not observed in chronic sinusitis. After 7.6 months postoperatively, samples were taken from the same sites and examined using scanning electron microscopy. The mean postoperative ciliary area value was 74% in the superolateral wall and 51% in the ostium. These postoperative values were significantly higher than the preoperative values. These results suggest that loss of cilia in chronic sinusitis is a reversible phenomenon. However, those with low ciliary area at the time of surgery did not recover to the same extent as those with higher ciliary area.

Unlike allergic rhinitis, nasal mucosal sensitivity to histamine is not enhanced in chronic sinusitis. We instilled a histamine solution with serial dilution on the inferior nasal mucosa until sneezing occurred. There was no significant difference in the histamine threshold between chronic sinusitis patients and normal control subjects. Thus epithelial abnormalities in chronic sinusitis are not severe enough to cause enhanced mucosal reactions to environmental stimuli as in the case of asthma.

Recently, Ponikau et al. reported that epithelial damage (shedding) was observed in all specimens from twenty-two randomly selected patients with refractory chronic rhinosinusitis undergoing endoscopic sinus surgery. The discrepancy between the results in this study and our observations may come from differences in subtype classification of sinusitis. Since 68% of their subjects had been previously diagnosed with asthma, most of their patients had diagnoses of chronic hyperplastic eosinophilic sinusitis according to the classification explained in the introduction. On the other hand, the majority of our subjects had chronic inflammatory sinusitis.

MUCOSAL THICKENING AND SUBEPITHELIAL FIBROSIS

Electron microscopy of asthmatic basement membrane demonstrated that the true basement membrane, the lamina rara and densa, is normal in these tissues. The “thickening” is the result of a dense fibrotic response that occurs primarily in the lamina reticularis. This response is characterized by the enhanced accumulation of fibronectin and types I, III, and V collagen. In chronic sinusitis, mucosa in the maxillary sinus is thickened. Sobol et al. examined submucosal collagen deposition using van Gieson stain. The mean grade of subepithelial collagen deposition was significantly higher in adult patients with chronic sinusitis and pediatric patients compared with control subjects. Although the presence of subepithelial fibrosis has been associated with disease severity and correlated with a decline in FEV1 in asthma, significance of subepithelial collagen deposition in chronic sinusitis is not known.

GLAND CELL METAPLASIA

Mucus hypersecretion is a well-documented feature of chronic sinusitis. In humans, subepithelial glands are the major source of airway mucus. In order to determine whether goblet cells or submucosal gland cells are important in chronic sinusitis, Majima et al. histochemically quantitated the number of goblet cells and submucosal acinar cells in the nasal mucosa from 65 patients with chronic sinusitis and 18 normal control subjects. Results showed no significant difference in the number of goblet cells between normal controls and chronic sinusitis. On the other hand, the number of submucosal acinar cells in chronic sinusitis was significantly higher than that in normal controls (p<0.01). The area occupied by the acini in lamina propria was also increased in chronic sinusitis (p<0.001). This was also true in the case of maxillary sinus. Thus, hyperplasia and hypertrophy of nasal acinar cells may have an important role in mucus hypersecretion in chronic sinusitis.

In order to more clearly determine the nature of the mechanism of submucosal gland hyperplasia and hypertrophy, Guo et al. established a serum-free three dimensional culture system for human nasal gland cells and Kimura et al. examined the effects...
of epidermal growth factor, keratinocyte growth factor, and retinoic acid on proliferation and differentiation of these cells. The addition of EGF promoted the proliferation of human nasal gland cells in its optimal concentrations, and KGF also enhanced cell proliferation. Conversely, cell differentiation was not dependent on EGF and KGF. Lee et al. identified EGF-R in submucosal gland cells and determined immunoreactivity for EGF in epithelial cells, inflammatory cells and in some submucosal gland cells. The finding that EGF-R and its ligand proteins in chronic sinusitis specimens stain stronger than in controls suggests that EGF and EGF-R are involved in proliferation of submucosal gland cells. Furthermore, KGF and its receptor mRNAs are upregulated in chronic sinusitis.

**REMODELING IN NASAL POLYPS**

Nasal polyposis is a chronic inflammatory disease of the nasal mucosa with inflammatory cells, infiltration, especially eosinophil, and structural modifications of the epithelium (secretory hyperplasia and squamous metaplasia) and lamina propria (basement membrane thickening, extracellular matrix accumulation and fibrosis). Although the pathophysiology of nasal polyps is not clearly known, our hypothesis on the formation of nasal polyps is shown in the Figure 1.

Kakoi and Hiraide classified nasal polyps as soft tissue masses of edematous (60%), glandular-cystic (27%) and fibrous (13%) types, which exhibit intact epithelium on the surface with massive edema fluid, and pseudocyst formation in the deeper layers. Polyp tissue seems to be significantly denervated, and it is postulated that the open endothelial junctions of venules might be responsible for the vascular leakage. However, the pathophysiological mechanisms of the formation and growth of nasal polyps remain poorly understood.

The following is an explanation of epithelial abnormality, subepithelial fibrosis, gland abnormality, and infiltrating cells.

**EPITHELIAL ABNORMALITY**

Nasal polyps have extremely diverse histogical findings. Although squamous metaplasia and goblet cell hypertrophy was observed in many patients, epithelial shedding, which is characteristic of asthma, was not observed in nasal polyps.

**SUBEPITHELIAL FIBROSIS**

Histochemical analysis revealed deposition of types I, III, and V collagens. Fibrosis is a dynamic process that involves a balance of matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). We postulated that expression of MMPs are involved in the formation and growth of nasal polyps and examined the expression of MMP-2 and MMP-9. Using RT-PCR, we found that MMP-2 mRNA but not MMP-9 mRNA was expressed in nasal polyps. However, neither of these proteins were expressed in the inferior turbinate of the healthy subjects. We confirmed the expression of the MMP-2 protein using a monoclonal antibody against MMP-2. MMP-2 immunostaining was observed in subepithelial cells and basal cells of the epithelia in nasal polyps. We postulated that cells having positive signals in the subepithelial area are probably fibroblasts. There was no evidence of MMP-2 immunostaining in the inferior turbinates of patients with allergic rhinitis.

In contrast, Lechapt-Zalman et al. reports different findings regarding MMP expression. In their study, MMP-2 and MMP-9 expression in the nasal polyps of 24 patients undergoing ethmoidectomy was compared with 15 control nasal mucosal samples obtained from snorers during turbinectomy. Concomitant studies of gelatinase immunoexpression showed that MMP-9 expression was enhanced (4- to 16-fold) in surface epithelium, glands (p<0.05), and submucosal inflammatory cells (p<0.05). In addition, MMP-9 positivity was markedly increased in endothelial cells (p<0.01). These results suggest up-regulation of MMP-9 expression in the glands and vessels of nasal polyps. The investigators concluded that MMP-9 may play a role in upper airway remodelling during nasal polypsis. However, despite the fact that MMP-2 expression in nasal polyps was higher than that in nasal mucosa, there was no statistical difference. Although there is some discrepancies between the results in our study and their results, it can be concluded that specific expression of MMP is important in the forma-
inflammatory cells controlled by TGF-beta, which is produced locally by
opment of myofibroblasts in nasal polyps could be
tion. The investigators concluded that the local devel-
osal polyps by inducing extracellular matrix accumula-
blasts, which are abundant in nasal polyps but rare in
SMA positivity. It can be postulated that myofibro-
nificantly more numerous in the pedicle than in the tip
areas, whereas TGF-beta-positive cells were signifi-
cosmula. Furthermore, in the eight selected nasal polyps,
significantly higher in nasal polyps than in nasal mu-
sone cells is observed in the gland. Furthermore, the
glands are much larger than those observed in
chronic sinusitis mucosa. Cysts are often seen in the
They contain eosinophilic contents. It can be
assumed that mucin produced in the glands can not
be secreted effectively. Thus gland acinar cells and
cells in the conducting tubules undergo degenera-
tion, forming a cyst.

INFILTRATING CELLS
Although cell infiltration is not a part of remodeling, it
is important to stress that eosinophil infiltration in the
nasal polyps is one of the key players in its patho-
geneses. Subepithelial eosinophil number is much
greater in the nasal polyps than that in the inferior
turbinate of patients with chronic sinusitis.
The importance of eosinophilic inflammation is
well investigated by Bachert et al.21 They sought to
determine whether there is an association between
total and specific IgE to a variety of allergens in polyp
and nonpolyp tissue and markers of eosinophilic
flammation or skin test results. The concentrations of
total IgE, IL-5, eotaxin, ECP, LTC4/D4/E4, and sCD23
were significantly higher in nasal polyp tissue com-
pared with nonpolyp tissue. Total IgE correlated sig-
ificantly with IL-5, ECP, LTC4/D4/E4, and sCD23 and
with the number of eosinophils in nasal polyps.
They concluded that there is an association between
increased levels of total IgE, specific IgE, and eosino-
philic inflammation in NPs, which may be of rele-
vance in the pathophysiology of nasal polyposis. How-
ever, some of the polyps do not contain many eosino-
phils, while mononuclear cells are the dominant cell
types in the infiltrating cells. The mechanism of for-
formation and development of such mononuclear cell
dominant polyps are poorly understood and should
be investigated in the future.

CONCLUDING REMARKS
There is clear distinction between remodeling in

### Table 1 Remodeling in asthma, chronic sinusitis and nasal polyps

<table>
<thead>
<tr>
<th>Change</th>
<th>Asthma (Djukanovic22)</th>
<th>Chronic sinusitis</th>
<th>Nasal polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial shedding or loss</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>Increased collagen deposition</td>
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<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Increased microvasculature</td>
<td>present</td>
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<td>unknown</td>
</tr>
<tr>
<td>Hypertrophy and hyperplasia of submucosal glands</td>
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<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Goblet cell metaplasia</td>
<td>present</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Hypertrophy and hyperplasia of smooth muscle</td>
<td>present</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>Changes of adventitia</td>
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</tr>
</tbody>
</table>
asthma and that in chronic sinusitis and nasal polyps. Characteristics of remodeling in the three diseases are summarized in the Table 1. In the chronic sinusitis, epithelial shedding, which is a characteristic of asthma, is not observed in the maxillary sinus. The increase of mirovillous cells, squamous metaplasia, and goblet cells is observed in many patients with chronic sinusitis. Although accumulation of extracellular matrix is a main feature of nasal polyps, its pathogenesis is not clearly known. This should be clarified in future studies.

REFERENCES