

Effect of topical rebamipide on goblet cells in the lid wiper of human conjunctiva

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Received October 25, 2016; Accepted December 7, 2016

DOI: 10.3892/etm.2017.4390

Abstract. It has been demonstrated that topical administration of rebamipide, which is an antiulcer agent, increases the mucin level of the tear film and ameliorates ocular surface conditions such as lid wiper epitheliopathy. The aim of the present study was to analyze the changes in goblet cell number, cell proliferation, and epidermal growth factor receptor (EGFR) induced by topical rebamipide addition to the lid wiper of humans. A total of 30 eyelid tissue samples were obtained during involutional entropion surgeries, fixed in paraformaldehyde, embedded in paraffin and divided into two groups: Rebamipide or non-rebamipide. The tissues in the rebamipide group were obtained from patients who had a medical history of topical rebamipide use prior to surgery. The number of goblet cells was counted under light microscopy. A total of 22 eyelid tissue samples were further examined using immunohistochemistry with anti-Ki-67 and anti-EGFR antibodies to evaluate cell proliferation and EGFR expression, respectively. Histologically, the lid wiper and palpebral conjunctiva were clearly identified in the tissues. The number of goblet cells was significantly higher in the rebamipide group compared with the non-rebamipide group ($P=0.0367$). There was no significant difference in lid wiper cell proliferation between the rebamipide and non-rebamipide groups. Immunohistochemistry revealed that EGFR levels in the lid wiper epithelial cells were significantly higher in the rebamipide group compared with the non-rebamipide group ($P=0.0237$). These results suggest that topical rebamipide application increases the number of goblet cells in the lid wiper, which in turn upregulates the expression of EGFR. These findings may be clinically relevant and provide a therapeutic

basis for the treatment of ocular disease such as dry eye and lid wiper epitheliopathy.

Introduction

The lid wiper is a part of the conjunctiva, located at the inner lid border of the upper and lower eyelids (1,2). Due to its location, the lid wiper represents the zone of the lid margin that wipes over the bulbar conjunctiva and the cornea during blinking. Histologically, the lid wiper is an epithelial thickening where mucin-secreting goblet cells are intermingled (2). Goblet cells contribute to the maintenance of the normal precorneal tear film (3) and also the internal lubrication system for reduction of friction between the lid margin and the globe (2). Clinically, goblet cell damage in the lid wiper may induce deterioration in mucin secretion and friction, which lead to several ocular surface disorders such as dry eye and lid wiper epitheliopathy (4,5).

It has previously been demonstrated that topical administration of rebamipide, an antiulcer agent, increases the mucin level of the tear film and improves the conditions of the ocular surface in dry eyes (6) and lid wiper epitheliopathy (4). Previous studies have reported that rebamipide facilitates the secretion of mucin. Rebamipide has been found to increase the number of goblet cells in the bulbar conjunctiva of rabbits *in vivo* (7). Rios *et al* (8) demonstrated that rebamipide has the ability to proliferate cultured rat conjunctival goblet cells. In another study, topical rebamipide application significantly improved corneal epithelial damage via enhancing the expression of mucin *muc5* mRNA on the murine ocular surface (9). Previous findings showed that topical rebamipide may increase the number of goblet cells and promote the secretion of mucin-like substances in the bulbar conjunctiva and lacrimal caruncle of humans (10,11). However, to the best of our knowledge, there are no reports involving histological examination of the alteration of goblet cell numbers in human lid wiper associated with topical rebamipide application.

Epidermal growth factor receptor (EGFR), a cell surface protein, binds to epidermal growth factor, which induces receptor dimerization and tyrosine autophosphorylation (12). These cascades drive multiple cellular responses, such as cell proliferation and differentiation (12). The EGFR-signaling pathway serves an important role in goblet cell proliferation

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Key words: rebamipide, goblet cells, lid wiper, epidermal growth factor receptor, humans

and mucin secretion from the cells. EGFR signaling contributes to the underlying mechanisms of goblet cell metaplasia and mucus hypersecretion in the epithelia of human airways (13). Several previous studies have demonstrated that transactivation of EGFR enhances mucin secretion in rat conjunctival goblet cells (14-16). Furthermore, Rios *et al* (16) demonstrated that topical rebamipide stimulates mucin secretion from cultured goblet cells via the EGFR-signaling pathway.

The aim of the present study was to examine the number of goblet cells in the lid wiper of humans, and to analyze changes in goblet cell number and cell proliferation as a result of topical rebamipide administration. EGFR expression in the lid wiper was also investigated to establish whether there is a correlation between goblet cell number and mucin secretion.

Materials and methods

Patients. A total of 28 patients with involutional lower eyelid entropion, conjunctival dysplasia, and nevus of the lacrimal caruncle were enrolled in the present study between January 2011 and November 2014. The 26 patients with involutional lower eyelid entropion consisted of 5 females and 21 males and all provided their written informed consent. Unilateral and bilateral entropion were observed in 22 and 4 cases, respectively. The patients' age ranged from 60-90 years (mean, 76.4 years). Usage of preoperative topical eye drops and/or ointment and the duration of the usage were retrospectively recorded based on medical records. The patients were subsequently divided into rebamipide (7 patients) or non-rebamipide (19 patients) groups. It has previously been demonstrated that topical rebamipide application improves the objective symptoms of dry eyes in patients within 2 weeks (17); the rebamipide group therefore consisted of patients who had used 2% topical rebamipide eye drops for >2 weeks prior to surgery, and the non-rebamipide group comprised patients who had not used topical rebamipide or had used it for <2 weeks prior to surgery. The tissues examined in the present study included conjunctival and lacrimal caruncle tissues. In this study, patients with entropion ciliarum, trichiasis, Stevens-Johnson syndrome and ocular pemphigoid were excluded in this study. The present study was approved by the institutional review boards of Teine Keijinkai Hospital (Sapporo, Japan), Abashiri Kousei Hospital (Abashiri, Japan), and Hokkaido University Hospital (Sapporo, Japan), and is adherent to the tenets of the Declaration of Helsinki.

Isolation of eyelid tissue during involutional entropion surgery. A total of 30 eyelid tissue samples were isolated using the modified Quickert method (18) for involutional entropion (Fig. 1). Briefly, a subciliary skin incision was made following the administration of local anesthesia using 2% xylocaine injection with epinephrine (AstraZeneca, Osaka, Japan) with 1.5 ml lidocaine supplemented with 2% epinephrine (Fig. 1A). Eyelid tissues including the anterior and posterior lobes and measuring 4-5 mm were excised using scissors to reduce the horizontal laxity (Fig. 1B and C). The resected tissues were immediately fixed in 4% paraformaldehyde at room temperature in the operating room. Divided eyelid tissues were connected by suturing with each tarsal plate using 6-0 polypropylene (Fig. 1D). Subcutaneous tissues and tarsal plates

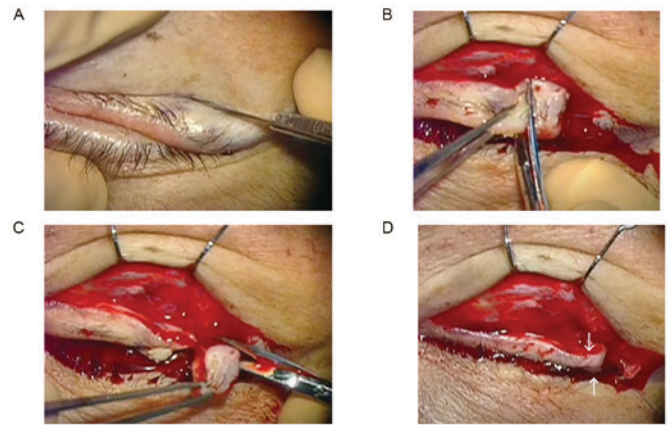


Figure 1. Isolation of the eyelid tissue during involutional entropion surgery. (A) Following the administration of local anesthesia, subciliary skin incision is performed. (B and C) All layers of the eyelid tissue are excised. (D) Deficit eyelid tissues are connected by suturing with each tarsal plate using 6-0 polypropylene (arrows).

were then sutured with 8-0 vicryl to correct the direction of cilia. Incised eyelid skin was finally sutured with 6-0 polypropylene, and the suture was released 1 week post-surgery. All surgeries were conducted by a single ophthalmologist at Teine Keijinkai Hospital and Abashiri Kousei Hospital.

Hematoxylin and eosin (H&E) staining, periodic acid Schiff (PAS) staining with diastase digestion and immunohistochemistry. Approximately 2 days after fixation, formalin-fixed tissues were embedded in paraffin. The serial tissue sections were cut to a thickness of 4 μ m and were used for H&E staining, PAS staining with diastase digestion, and immunohistochemistry. The number of goblet cells morphologically confirmed by H&E staining in the lid wiper and palpebral conjunctiva was counted under a light microscope (magnification, x40) in one or two fields on each slide, and the mean was calculated. Goblet cells located in the crypts of palpebral conjunctiva were not evaluated in the present study. For immunohistochemistry, microwave-based antigen retrieval was performed in 10 mM citrate buffer (pH 6.0; Roche Diagnostics, Basel, Switzerland) as a pretreatment. The sections were incubated with 3% hydrogen peroxide (Roche Diagnostics) for 4 min at 37°C to block endogenous peroxidase activity. The sections were subsequently incubated overnight at 4°C with anti-EGFR antibody (undiluted; cat. no. 518-102432; Roche Diagnostics), or anti-Ki-67 antibody (1:50 dilution; cat. no. M7240; Mib-1; Dako; Agilent Technologies, Inc., Santa Clara, CA, USA). Positive signals in each section were visualized using diaminobenzidine (Roche Diagnostics; Ventana Benchmark ULTRA, ultra-view 760-500). Positive signals were determined using a microscope (Olympus BX51; Olympus Corp., Tokyo, Japan). Positive controls were selected from lung carcinomas, which were previously stained positive and clinically diagnosed as ERGR-positive lung cancer by a clinical physician. For negative controls, primary antibodies were replaced by PBS.

To evaluate EGFR expression, membranous staining in the epithelia of the lid wipers or palpebral conjunctiva was scored using a four-grade scale (0, 1, 2 or 3), which was modified according to a previous report (19). The following

scoring criteria were used: Grade 0, if <10% of the epithelial cells showed membranous immunoreactivity for EGFR; grade 1, membranous immunoreactivity was present in >10, <50% of the epithelial cells; grade 2, if membranous immunoreactivity was present in >50, <90% of the epithelial cells; and grade 3, if >90% of the epithelial cells had strong staining on the membrane. In the present study, grades 0 and 1 were evaluated as EGFR-negative, whereas grades 2 and 3 were EGFR-positive. For Ki-67, immunopositive nuclei and the total number of epithelial cells were directly counted under light microscopy (magnification, x40) in one or two fields, and then percentage of immunopositive cells was calculated and represented as Ki-67 index (%) in each case. Two raters, who were blinded to the clinical information, scored the immunostaining.

Statistical analysis. The statistical analyses were conducted by statistical analysis software, Ver. 2.0, for Macintosh (Statistics Survey System-development; Esumi Corporation, Tokyo, Japan). The Mann-Whitney U test was applied to examine the correlation between the number of goblet cells and Ki-67 index in the lid wiper and palpebral conjunctiva in the rebamipide and non-rebamipide groups. The correlation between duration of topical rebamipide use and the number of goblet cells was evaluated using the Spearman correlation coefficient. The Chi-square test was applied for correlation between EGFR-positivity and rebamipide and non-rebamipide groups. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Histological findings of the eyelid excised during entropion surgery. Histologically, the lid wiper and palpebral conjunctiva as well as skin of the eyelid, and muco-cutaneous junction (MCJ) were clearly defined in all of the tissues examined (Fig. 2A). The lid wiper, palpebral conjunctiva, MCJ, eyelid skin, meibomian glands and dermal papilla were clearly identified (Fig. 2B) in the excised eyelid tissue with magnified lid wiper (Fig. 2B: black box) and palpebral conjunctiva (Fig. 2B: blue box). The lid wiper demonstrated thickened conjunctiva, which was located near the MCJ along with the palpebral conjunctiva (Fig. 3A-F). Goblet cells in the specimens all had abundant cytoplasm, containing a mucin-like substance and with flattened nuclei; goblet cells formed clusters in the lid wiper of the conjunctiva or in the superficial layer of the columnar epithelium. PAS staining with diastase digestion facilitated recognition of mucin within goblet cells (Fig. 3E and F). These morphological findings were consistent with the findings in goblet cells of the cadaver eyelid as reported previously (2). In contrast, palpebral conjunctiva contained the relatively flattened columnar epithelium, in which several goblet cells were intermingled (Fig. 2, lower right panel). The number of goblet cells was 16.2 ± 13.2 and 6.2 ± 4.4 in the lid wiper and palpebral conjunctiva, respectively, of all the eyelids in the rebamipide and non-rebamipide groups. The number of goblet cells was significantly higher in the lid wiper than that of palpebral conjunctiva in all the eyelids ($P < 0.01$).

Comparison of goblet cells in rebamipide and non-rebamipide groups. Based on the medical records of patients, tissue samples

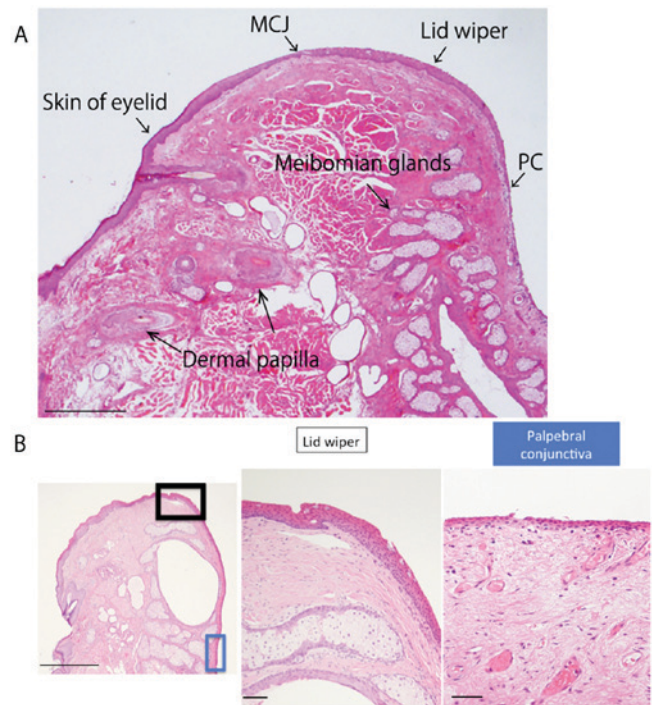


Figure 2. Histology of eyelid tissue from a patient in the non-rebamipide group during entropion surgery. (A) The lid wiper, PC, MCJ, eyelid skin, meibomian glands and dermal papilla are clearly identified (magnification, x50). (B) Eyelid tissue with magnified lid wiper (black box) and PC (blue box). Left panel, magnification of x50; center and right panels, magnification of x100. PC, palpebral conjunctiva; MCJ, muco-cutaneous junction. Scale bar, 100 μ m.

were divided into the rebamipide (n=9) and non-rebamipide (n=21) groups. There was no significant difference in patient age between these groups. Of the 21 eyelid tissues in the non-rebamipide group, 3 were not treated with any topical agents prior to surgery, and were considered control eyelids. The remaining 18 eyelids had been treated with topical hyaluronic acid, antibiotics, non-steroidal anti-inflammatory agents, eye drops against lacrimation, and/or ointments. In the rebamipide group, the duration of topical rebamipide use prior to surgery was 23-55 days (mean, 38 days). The number of goblet cells in the lid wiper was found to be 29.4 ± 13.8 and 12.2 ± 9.4 in the rebamipide and non-rebamipide groups, respectively (Fig. 3). The number of goblet cells in the lid wiper was significantly higher in the rebamipide group compared with the non-rebamipide group ($P = 0.0367$). The number of goblet cells in the palpebral conjunctiva was 4.9 ± 3.4 and 6.8 ± 4.7 in the rebamipide and non-rebamipide groups, respectively, with no significant difference observed. In the rebamipide group, there was no significant correlation between the duration of rebamipide use and the number of goblet cells present.

Immunohistochemical results on Ki-67 and EGFR. A total of 8 eyelid tissues from the rebamipide and 14 from the non-rebamipide groups were analyzed immunohistochemically. Nuclear immunoreactivity for Ki-67 was clearly observed in the epithelia of the lid wiper (Fig. 4A) and palpebral conjunctiva (Fig. 4B) in the rebamipide group. The Ki-67 index was 8.9 ± 5.1 and 2.4 ± 1.0 in the epithelia of lid wipers and

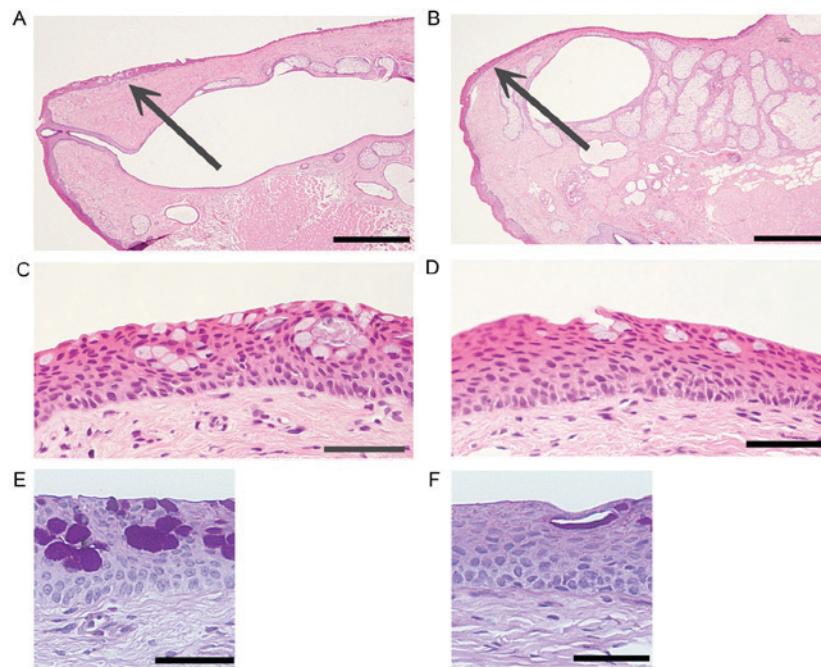


Figure 3. H&E staining and PAS staining with diastase digestion in eyelid tissues treated with or without topical rebamipide. H&E staining with arrows indicating the lid wiper in tissues from the (A) rebamipide and (B) non-rebamipide groups. Magnified lid wipers from the (C) rebamipide and (D) non-rebamipide groups. The number of goblet cells is greater in the (E) rebamipide group than the (F) non-rebamipide group. PAS staining with diastase digestion reveals mucin within the epithelium. More mucin is present in the rebamipide group. H&E, hematoxylin and eosin; PAS, periodic acid-Schiff. Scale bar, 50 μ m (A and D, magnification, x50; B, C, E and F, magnification, x200).

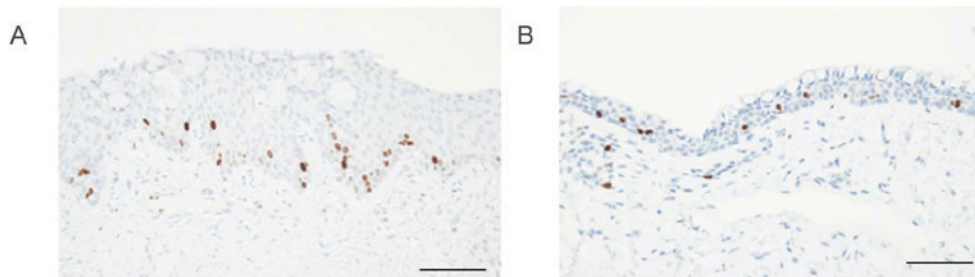


Figure 4. Immunoreactivity for Ki-67 in (A) the lid wiper and (B) the palpebral conjunctiva of a human eyelid in the rebamipide group. Nuclear immunoreactivity for Ki-67 can be observed in the epithelial cells. The number of Ki-67-positive cells is higher in the lid wiper than in the palpebral conjunctiva. Bars indicate 50 μ m (magnification, x200).

Table I. Comparison of rebamipide and non-rebamipide groups in Ki67 index in the epithelia of lid wiper and palpebral conjunctiva.

Location	Number of cases	Mib-1 index	P-value
Lid wiper			0.22
Rebamipide	8	10.5 \pm 4.2	
Non-rebamipide	14	7.9 \pm 3.8	
Palpebral conjunctiva			0.14
Rebamipide	8	2.8 \pm 1.8	
Non-rebamipide	14	2.1 \pm 0.0	

palpebral conjunctiva, respectively, in all the tissues examined. The Ki-67 index in the lid wiper was significantly higher than

in the palpebral conjunctiva ($P < 0.01$). However, no significant difference was observed in the Ki-67 index between the rebamipide and non-rebamipide groups, regardless of location (Table I).

EGFR immunoreactivity was noted in the basal layers of the epithelium in eyelid skin and conjunctiva, and in the meibomian gland in all tissues examined. Immunoreactivity for EGFR in the epithelial cells of the lid wiper and palpebral conjunctiva varied between eyelids (Fig. 5). In one non-rebamipide group tissue sample, <10% of the epithelial cells presented membranous expression, and it was evaluated as grade 0 (Fig. 5A). In another non-rebamipide tissues, faint cytoplasmic immunoreactivity was observed, however <50% of epithelial cells had membranous immunoreactivity for EGFR, and so it was evaluated as grade 1 (Fig. 5B). In a third non-rebamipide tissue sample, <90% of epithelial cells revealed membranous immunoreactivity for EGFR, which was thus evaluated as grade 2 (Fig. 5C). In a rebamipide tissue

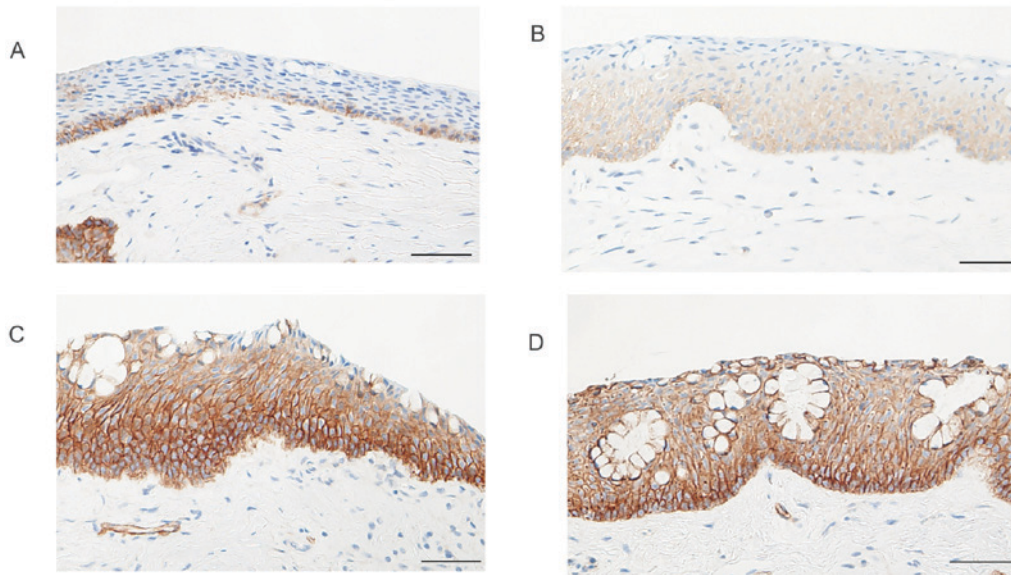


Figure 5. Immunoreactivity for EGFR in the lid wiper of eyelid tissues. (A) <10% of the cells are positive for EGFR in tissue from a non-rebamipide patient evaluated as grade 0. (B) <50% of cells are positive for EGFR, in another non-rebamipide patient evaluated as grade 1. (C) <90% of epithelial cells are positive for EGFR in tissue from a non-rebamipide patient, evaluated as grade 2. (D) Almost all epithelial cells and goblet cells show strong membranous immunoreactivity for EGFR in tissues from a patient in the rebamipide group, evaluated as grade 3. EGFR, epidermal growth factor receptor. Scale bar, 50 μ m (magnification, x200).

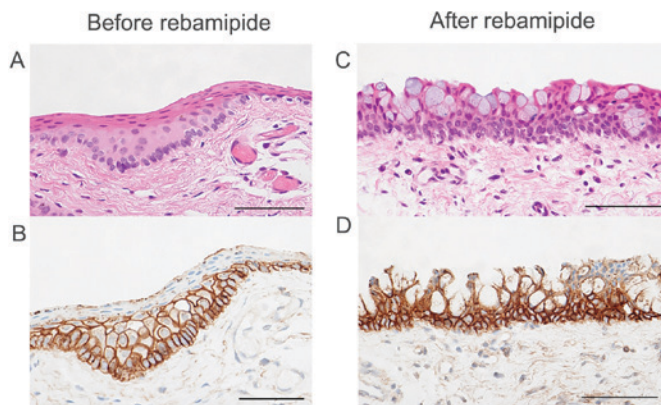


Figure 6. EGFR expression in (A and B) non-cancerous bulbar conjunctival tissues in a patient with mild dysplasia and (C and D) at the same site 3 months after topical rebamipide was started, as previously reported (10). (B) Prior to rebamipide use, EGFR immunoreactivity was predominantly detected in the basal and suprabasal layers of the epithelium. (D) Notably, EGFR expression was upregulated in the epithelia following topical rebamipide use. H&E, hematoxylin and eosin; EGFR, epidermal growth factor receptor. Bars indicate 50 μ m (magnification, x200).

sample, almost all epithelial cells and goblet cells displayed strong membranous immunoreactivity for EGFR, which was evaluated as grade 3 (Fig. 5D). All 8 lid wipers in the rebamipide group were positive for EGFR, whereas only 9 out of 14 lid wipers in the non-rebamipide group were EGFR-positive. The number of EGFR-positive lid wipers in the rebamipide group was significantly higher than in non-rebamipide group (Table II; $P=0.0237$). EGFR-positive goblet cells were also intermingled in the epithelia of the lid wiper in the rebamipide group (Fig. 5D). EGFR expression was further examined in the bulbar conjunctival tissue and a lacrimal caruncle tissue of humans, as previously reported (10,11). We have shown that an increased number of goblet cells were observed following

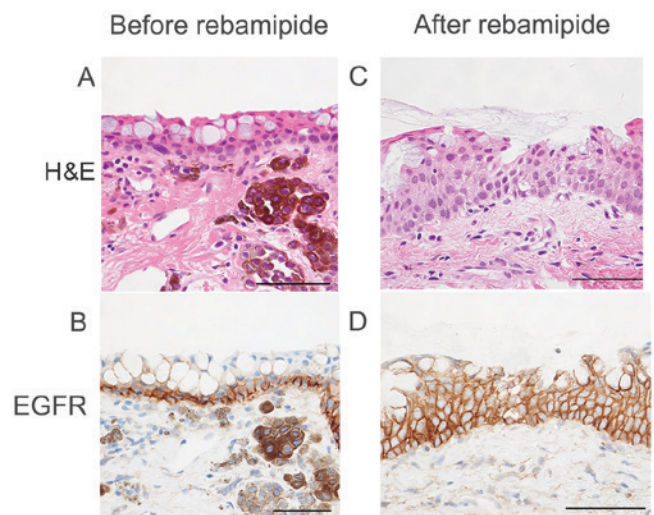


Figure 7. EGFR expression in (A and B) lacrimal caruncle tissues in a patient with nevus and (C and D) at the same site 3 months following topical rebamipide was initiated, which was previously reported (11). (B) Prior to rebamipide use, EGFR immunoreactivity was observed in the basal layer of the epithelium. (D) Notably, EGFR expression is upregulated in the epithelia following topical rebamipide use. H&E, hematoxylin and eosin; EGFR, epidermal growth factor receptor. Bars indicate 50 μ m (magnification, x200).

treatment with topical rebamipide in human tissues (10,11). Notably, EGFR expression was upregulated in the epithelia 3 months following topical rebamipide use compared with prior to treatment (Figs. 6 and 7). No significant difference was observed in EGFR-positivity in the palpebral conjunctival epithelia between groups. Taken together, Fig. 8 demonstrates the schema of presumed mechanisms underlying mucin secretion by rebamipide. Topical rebamipide led to EGFR expression in epithelial cells of the ocular surface, which

Table II. The number of EGFR positive or negative eyelids in the lid wiper and palpebral conjunctiva.

Group	Lid wiper, n		P-value	Palpebral conjunctiv, n		P-value
	EGFR+	EGFR-		EGFR+	EGFR-	
Rebamipide	8	0	0.0237	4	4	>0.05
Non-rebamipide	9	5		7	7	

EGFR, epithelial growth factor receptor; +, positive; -, negative.

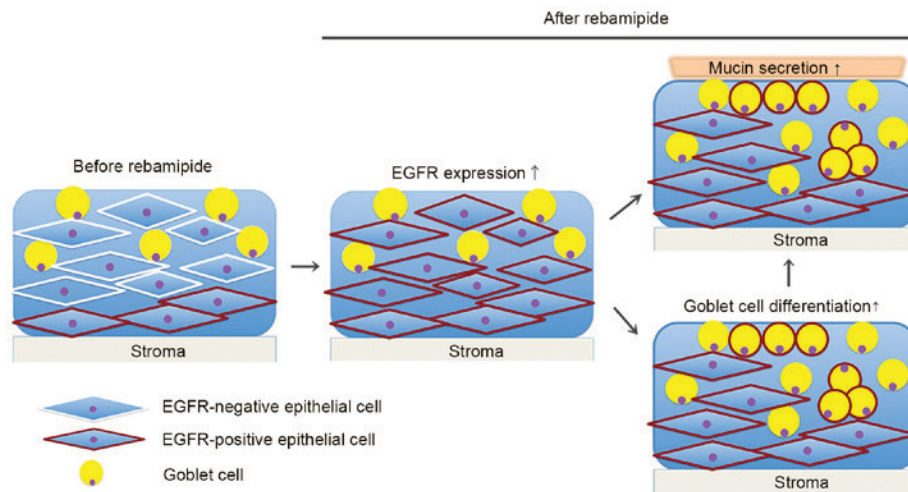


Figure 8. Effect of topical rebamipide on goblet cells and subsequent mucin secretion in the lid wiper. Topical rebamipide induces EGFR expression in epithelial cells, which leads to goblet cell differentiation and an increased number of goblet cells. The increase in goblet cells subsequently promotes the secretion of mucin to the ocular surface. In addition, EGFR upregulation may also stimulate mucin secretion from the goblet cells. EGFR, epithelial growth factor receptor.

resulted in goblet cell differentiation and an increased number of goblet cells. The increase in goblet cells subsequently promoted the secretion of mucin to the ocular surface. EGFR upregulation may stimulate mucin secretion from the goblet cells (Fig. 8).

Discussion

Historically, pathological investigations on the lid wiper have been limited as there are few opportunities to isolate and evaluate the lid wiper tissues in clinical ophthalmology. Histological findings of the lid wiper were initially reported in ocular tissues from human cadavers (1,2). In the present study, 30 eyelid tissues that were surgically removed due to involutional entropion, and in which the lid wiper and palpebral conjunctiva could be analyzed pathologically, were examined. The histological findings of these isolated tissues were similar to those in the cadaver eyes, as reported previously (1,2). To the best of our knowledge, this is the first report presenting histopathological examination of the lid wiper surgically removed in living human patients. Notably, the number of goblet cells was found to be significantly higher in the lid wiper than the palpebral conjunctiva. The histological data demonstrating goblet cell distribution in the lid wiper may support a previous report that goblet cells are associated with the reduction of friction during blinking (2). Furthermore, the Ki-67 index in the epithelia of the lid wiper

was significantly higher than that of the palpebral conjunctiva. These observations suggest that epithelial hyperplasia may occur in the lid wiper as a result of chronic stimulation by everyday blinking, indicating that the lid wiper may be an essential site for maintenance of the healthy ocular surface.

The authors of the present study previously reported that the number of goblet cells increased following topical rebamipide application to the bulbar conjunctiva and lacrimal caruncle of humans (10,11). These results suggest that rebamipide serves an important role in increasing the number of goblet cells, thereby releasing more mucin onto the ocular surface. In the present study, preoperative topical agents used were retrospectively established based on medical records prior to eyelid resection, and eyelid tissue samples were divided into two groups based on this. Notably, the number of goblet cells was significantly higher in the lid wiper of the rebamipide compared with the non-rebamipide group. However, no significant differences were observed in Ki-67 indices between the groups. These results suggest that topical rebamipide increases the number of goblet cells via cell differentiation within the epithelium rather than cell proliferation in the lid wiper.

Biologically, goblet cells are associated with the EGFR-signaling pathway, which results in goblet cell metaplasia and mucin secretion from the cells (13). In the present study, it was found that the number of EGFR-positive lid wipers was significantly greater in the rebamipide group compared

with the non-rebamipide group. Furthermore, it was found that EGFR expression was upregulated in the bulbar conjunctiva and lacrimal caruncle following topical rebamipide in humans. Rios *et al* (16) demonstrated that EGFR protein expression was upregulated following rebamipide addition in cultured rat goblet cells. Therefore, the data on EGFR induction in the lid wiper of the rebamipide group found in the present study are consistent with *in vitro* data published previously (16).

The presumed action of topical rebamipide on goblet cells in the human lid wiper was summarized in the present study. Topical rebamipide application induces EGFR expression in the epithelial cells, leading to goblet cell differentiation and an increased number of goblet cells, which subsequently promotes the secretion of mucin to the ocular surface. In addition, EGFR upregulation by rebamipide treatment may also directly stimulate mucin secretion from the goblet cells as reported previously (20).

In the present study, the effects of topical rebamipide on goblet cells were examined in two different sites of the eyelid; the lid wiper and palpebral conjunctiva. As stated above, there were significant differences in the number of goblet cells and EGFR-positivity in the lid wiper of rebamipide group compared with the non-rebamipide group, whereas no significant differences were noted in the palpebral conjunctiva despite preoperative topical rebamipide use. These results indicate that rebamipide does not always affect goblet cells, which may possess a different susceptibility to rebamipide depending on their location.

Kinoshita *et al* (17) recently reported the safety and efficacy of topical rebamipide use for 52 weeks in patients with dry eyes. Histologically, the results of the present study demonstrated that topical rebamipide is able to increase the number of goblet cells in humans; however, there are safety concerns on the extent of cell proliferation, which has not been addressed previously. In the present study, it was confirmed that topical rebamipide increased the number of goblet cells without inducing cell proliferation, as evaluated via the Ki-67 index. Furthermore, there was no correlation between the duration of topical rebamipide use prior to surgery and the number of goblet cells. Together, these histological observations indicate that goblet cell number and cell proliferation in the conjunctiva may be maintained within a set of limits, despite prolonged topical rebamipide use. Further study is required to clarify the long-term safety of topical rebamipide in human conjunctival tissues.

In conclusion, topical rebamipide increases the number of goblet cells in the lid wiper, which is correlated with an upregulation of EGFR. Topical rebamipide may contribute to the reduction of friction during blinking by inducing subsequent enhanced mucin secretion via the increased goblet cells.

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