The expression of Cathepsin L in oral lichen planus

Athip Kitkhajornkiat, Sorasun Rungsiyanont, Sineepat Talungchit, Pimporn Jirawechwongsakul, Patraya Taebunpakul*

Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, Srinakharinwirot University, Bangkok, Thailand

ARTICLE INFO

Keywords:

Lichen planus
Immunohistochemistry
Malignant transformation
Cathepsin

ABSTRACT

Background: Malignant transformation of oral lichen planus (OLP) was reported particularly in erosive type, however, it remains inconclusive. Cathepsin L was shown to promote tumor growth and invasion in many cancers. Therefore, cathepsin L expression in erosive and non-erosive OLP compared with oral epithelial dysplasia and oral squamous cell carcinoma (OSCC) were investigated.

Methods: Thirty specimens of OLP (15 cases each of erosive and non-erosive OLP), 10 cases of oral epithelial dysplasia and 10 cases of OSCC were included. Ten healthy gingiva specimens were served as controls. All specimens were stained with cathepsin L antibody using immunohistochemistry technique.

Results: Cathepsin L was expressed in all OLP and OSCC cases. In oral epithelial dysplasia and healthy gingiva, the expression was found at 90% and 50% respectively. The percentage of positive cells was the highest in erosive OLP ($27.26 \pm 12.09\%$), followed by non-erosive OLP ($20.85 \pm 7.43\%$), OSCC ($20.15 \pm 15.70\%$), oral epithelial dysplasia ($9.24 \pm 7.00\%$) and healthy gingiva ($2.27 \pm 5.65\%$). Most of non-erosive OLP cases showed mild staining intensity while erosive OLP and OSCC showed moderate staining intensity. Cathepsin L was mainly expressed at basement membrane zone and inflammatory cells of OLP. In OSCC, the expression was found in tumor islands and keratin pearls. In oral epithelial dysplasia and normal gingiva, cathepsin L expressions were low and presented in scattered pattern in both epithelium and connective tissue.

Conclusion: According to the patterns of expression in this study, cathepsin L could be implicated in pathogenesis and severity of OLP.

1. Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease involving oral mucosa. The prevalence is varied from less than 1% and up to 4%.¹ OLP mainly affects middle-aged people and commonly found in women. The etiology remains unclear. However, T-cell mediated autoimmunity is believed to play a role in pathogenesis of OLP.² Three major clinical manifestations of OLP have been defined namely reticular, atrophic and erosive. The present of mixed white and red lesions with ulcerations of OLP usually result in burning sensation and oral discomfort. Although OLP can spontaneously regress, many cases require treatment mainly using topical or systemic corticosteroids.^{2,3} A potential malignant transformation of OLP into oral squamous cell carcinoma (OSCC) has been suggested and discussed in literatures. Previous studies reported the rate of malignant change of OLP from 0.4% to 1.5%.⁴ However, some studies did not find any evidence of OLP transformation into OSCC. The long-term follow up of OLP lesions are

suggested. At present, there are no known markers to predict the malignant transformation of OLP.

Cathepsins are lysosomal proteases that control various normal biological processes, for instance, protein turnover, cell proliferation and cell death. Cathepsins participate in a number of processes in healthy cells.⁵ Besides, they also play a certain part in pathological processes like cancer progression.^{5,6} Cathepsin L, a member of cathepsin family, was found relevant for cancer progression of many neoplasms.^{7–10} Cathepsin L protein expression was related to the invasive and metastatic potential of OSCC.⁸ In addition, at mRNA level, overexpression of cathepsin L was detected in 48% of dysplastic lesions and in 64% of OSCC. An increase in cathepsin L protein was also found in a great number of dysplasia and cancers.¹¹

The studies of cathepsin L were only reported in skin lichen planus. It has been shown that the expression of cathepsin L was increased in skin lichen planus when compared with healthy skin specimens.¹² Another study reported no detection of cathepsin L in the epidermis of

* Corresponding author. Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, Srinakharinwirot University, Sukhumvit 23, Wattana, Bangkok, 10110, Thailand.

E-mail address: pthraya@g.swu.ac.th (P. Taebunpakul).

<https://doi.org/10.1016/j.jobcr.2020.06.003>

Received 17 April 2020; Received in revised form 21 May 2020; Accepted 14 June 2020

Available online 16 June 2020

2212-4268/ © 2020 Craniofacial Research Foundation. Published by Elsevier B.V. All rights reserved.

skin lichen planus.¹³ There has been no study on the expression of cathepsin L in OLP. Cathepsin L is frequently overexpressed in OSCC and was shown to be useful as a molecular marker of OSCC.^{6,8} In this study, we aim to investigate the expression of cathepsin L in non-erosive and erosive type of OLP compared with OSCC and oral epithelial dysplasia using immunohistochemistry technique. The results may help to understand the roles of cathepsin L in OLP and the process of malignant changes.

2. Materials and methods

2.1. Samples

Fifty cases of paraffin embedded tissues including 15 cases of non-erosive OLP, 15 cases of erosive OLP, 10 cases of oral epithelial dysplasia (7 cases of moderate oral epithelial dysplasia and 3 cases of severe oral epithelial dysplasia) and 10 cases of OSCC (7 cases of well differentiated OSCC and 3 cases of moderate differentiated OSCC) were included in the study. All selected specimens were clinical and histologically diagnosed by oral medicine specialists and oral pathologists. Control specimens ($n = 10$) were healthy gingival tissues, obtained during the third molar surgical removal process from volunteers, who granted written informed consent. The research project was approved by the Ethical Committee for Research in Human Subjects, no. SWUEC/E-085/2562.

2.2. Immunohistochemistry

The immunohistochemistry was performed using EnVision kit (Dako Agilent, USA). In brief, 4 μ m of paraffin-embedded sections were deparaffinized and rehydrated. Antigen retrieval was done in citrate buffer pH 6.0 microwaving (700 Watts) for 10 min. After 20 min of cooling down, endogenous peroxidase activity was blocked for 30 min incubation. Sections were washed with wash buffer and incubated with cathepsin L primary antibody (SC-32320, Santa Cruz Biotechnology, USA) at 4 °C overnight in moist chamber. The secondary antibody was added for 30 min. Sections were then washed thoroughly in wash buffer and the chromogen, 3,3'-Diaminobenzidine (DAB) was applied for 5 min. Sections were counterstained in hematoxylin for 5 min, dehydrated and mounted in Permount mounting medium. The human kidney was taken as positive control. For negative staining control, no primary antibody was added.

2.3. Interpretation of staining

The pattern of cathepsin L expression in each group was recorded. Besides, the specimens were analyzed and scored by two of the investigators (AK and SR) in consensus manner. The inter-investigator calibrations were performed with Cohen's kappa values equal to 0.94. Sixteen photographs were taken from each slide (including 8 areas from epithelium tissues and 8 areas from connective tissues) with a 400 $\times$ magnification using Motic Microscope camera. Cathepsin L positive cells were counted using Image J software. The data was analyzed on the basis of the percentage of cathepsin L positive cells and cathepsin L staining intensity (score 0–3). In addition, the immunoreactive score (IRS) was calculated as shown in Table 1.¹⁴

Table 1
Immunoreactive score.

Percentage of positive cells	Intensity of staining	IRS score IRS score = Percentage of positive cells $\times$ Intensity
0 = no positive cells	0 = no color reaction	0-1 = negative
1 = < 10% of positive cells	1 = mild reaction	2-3 = mild
2 = 10–50% positive cells	2 = moderate reaction	4-8 = moderate
3 = > 50–80% positive cells	3 = intense reaction	9-12 = strongly positive
4 = > 80% positive cells		

2.4. Statistical analysis

The statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The mean percentages of positive cells among groups were measured with One-way ANOVA. The results of IRS score between groups were evaluated with Chi-Square test. A p -value less than 0.05 were considered as statistically significant.

3. Results

Clinical data of all specimens are presented in Table 2. The ratio of male: female in OLP and oral epithelial dysplasia was at 1:5 and 1:1.5 respectively. While in OSCC, the male: female ratio was at 4:1. The mean age of each group was quite comparable except in healthy gingiva group. Cathepsin L was expressed in 100% of non-erosive OLP (15/15), erosive OLP (15/15) and OSCC (10/10) cases. In oral epithelial dysplasia and healthy gingiva, the expression was found at 90% (9/10) and 50% (5/10) respectively. The expression patterns and staining intensity were varied among groups. Cathepsin L expression in OLP was found in cytoplasm of epithelial cells as small granules pattern, while in connective tissues, the positive cathepsin L cells were mainly found in the nucleus of inflammatory cells near the basement membrane zone. There was no difference in cathepsin L expression pattern between erosive type of OLP and non-erosive type of OLP (Fig. 1). In oral epithelial dysplasia, cathepsin L expression was seen in both epithelium and connective tissues with low staining intensity. Most of the positive cells were observed in both nucleus and cytoplasm of epithelial cells. In connective tissues, the positive cells were mostly seen at the nucleus of inflammatory cells and fibroblasts (Fig. 2). In OSCC, cathepsin L expression was strongly expressed in tumor cells and keratin pearls. The expression was also observed at inflammatory cells in connective tissues (Fig. 3). In healthy gingiva, the specimens that expressed cathepsin L showed low staining intensity and can be seen in both epithelium and connective tissues.

3.1. The percentage of cathepsin L positive cells, the staining intensity and IRS score

Erosive OLP showed the highest percentage of positive cathepsin L cells ($27.26 \pm 12.09\%$), followed by non-erosive OLP ($20.85 \pm 7.43\%$) and OSCC ($20.15 \pm 15.70\%$) respectively. For oral epithelial dysplasia and healthy gingiva, the percentage of positive cells were found at $9.24 \pm 7.00\%$ and $2.27 \pm 5.65\%$ in that order (Table 3). There was a statistically significant difference between the percentage of positive cathepsin L cells in erosive OLP and oral epithelial dysplasia ($p < 0.05$) and in erosive OLP and healthy gingiva ($p < 0.05$). In contrast, there was no statistically significant difference in the percentage of positive cells between erosive and non-erosive OLP ($p = 0.078$) and between erosive OLP and OSCC ($p = 0.289$).

The staining intensity among groups were varied. Most of erosive OLP and OSCC cases showed moderate cathepsin L staining intensity with 60% and 50% respectively. The intense staining was observed only at 20% and 30% of erosive OLP and OSCC cases in that order. In contrast, the majority of non-erosive OLP cases (73.33%) and oral epithelial dysplasia cases (60%) showed mild staining intensity (Table 3).

The IRS score was also used to determine the expression of

Table 2
Clinical data of the population.

	Erosive OLP (n = 15)	Non-erosive OLP (n = 15)	Oral Epithelial Dysplasia (n = 10)	OSCC (n = 10)	Healthy gingiva (n = 10)
Age (years old)					
Mean $\pm$ SD	54.4 $\pm$ 11.92	51.73 $\pm$ 15.00	61.80 $\pm$ 14.45	58.40 $\pm$ 16.71	25.90 $\pm$ 8.06
Range	33–80	21–79	31–82	29–82	20–43
Gender					
Male	2 (13.33)	3 (20)	4 (40)	8 (80)	5 (50)
Female	13 (86.67)	12 (80)	6 (60)	2 (20)	5 (50)
Total	15 (100)	15 (100)	10 (100)	10 (100)	10 (100)
Site of lesions (n (%))					
Buccal mucosa	15 (100)	15 (100)	1 (10)	0 (0)	0 (0)
Tongue	0 (0)	0 (0)	6 (60)	3 (30)	0 (0)
Gingiva	0 (0)	0 (0)	1 (10)	2 (20)	10 (100)
Floor of mouth	0 (0)	0 (0)	0 (0)	4 (40)	0 (0)
Lip	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)
Palate	0 (0)	0 (0)	2 (20)	0 (0)	0 (0)

cathepsin L in the studied groups. Most of erosive type of OLP cases (73.33%) showed moderate IRS score. While 73.33% of non-erosive OLP cases were categorized as mild. The IRS scores between erosive and non-erosive OLP ($p = 0.019$) and between erosive OLP and oral epithelial dysplasia ($p = 0.030$) were statistically significant different. In addition, 80% of OSCC cases were categorized as moderate in IRS score. There was no statistically significant difference of IRS score between erosive OLP and OSCC ($p = 0.204$). All cases of healthy gingiva showed negative IRS score (Table 3).

4. Discussion

The prevalence of OLP malignant transformation in reports ranged from 0.4% to 1.5%.^{3,4} The risk factors associated with OLP transformation include erosive type of OLP, female gender and tongue site.¹⁵ The mechanisms responsible for OLP malignant transformation have not yet been recognized. It has been hypothesized that chronic inflammation together with oxidative stress are associated with OLP neoplastic changes by disturbing cell growth control.¹⁶

Cathepsin L, a lysosomal cysteine protease, is known to participate

Fig. 1. The expressions of cathepsin L in erosive OLP (A and B) and non-erosive OLP (C and D) were found mainly at the basement membrane zone and interface of epithelium and connective tissue (cathepsin L antibody, hematoxylin staining, $\times 100$ (A, C) and $\times 400$ (B, D), Epi = epithelium, CT = connective tissue).

Fig. 2. In oral epithelial dysplasia, cathepsin L was expressed in dysplastic cells and inflammatory cells in the connective tissue (cathepsin L antibody, hematoxylin staining, $\times 100$ (A, B, C, D), Epi = epithelium, CT = connective tissue).

in various biological processes including inflammation, bone resorption, cancer invasion and metastasis.^{5,6} Regarding the role of cathepsin L in human malignancies, the previous studies showed an increase in cathepsin L expression in epithelial dysplasias especially in cases with OSCC progression.¹¹ Cathepsin L was also shown to express in many types of human cancers. The use of cathepsin L as a prognostic marker for cancer metastatic and tumor recurrence has been reported.^{9,10,17,18} In our current study, we investigated the expression of cathepsin L in erosive and non-erosive OLP and compared with oral epithelial dysplasia, OSCC and healthy gingiva by using immunohistochemistry.

Prior studies reported that cathepsin L expression could be found in normal skin samples.^{19,20} Another group reported no detection of

cathepsin L in their normal skin specimens by immunohistochemistry. However, using qRT-PCR technique, they showed that cathepsin L was detected in all normal skin samples.¹³ In the present study, we found 50% of healthy gingiva specimens stained positive to cathepsin L but with low intensity. The rest of the samples did not express cathepsin L. The explanation could be that cathepsin L expression in some of our healthy gingiva samples was below a detectable level using immunohistochemistry technique.

Earlier studies reported that cathepsin L expression was related to the progression of OSCC and oral epithelial dysplasia.^{8,11} The number of patients with positive cathepsin L expression was shown to be higher in OSCC patients with nodal metastasis and clinical stage III or IV than

Fig. 3. The expression of cathepsin L in OSCC was found at the tumor islands (A, B, C) and in the connective tissue surface (D, E). Moreover, the strong cathepsin L expression was observed at the keratin pearls (F) (cathepsin L antibody, hematoxylin staining, $\times 100$ (A, E, F) and $\times 400$ (B, C, D)).

Table 3
The expression of cathepsin L.

	Erosive OLP	Non-erosive OLP	Oral Epithelial dysplasia	OSCC	Healthy Gingiva
Cathepsin L (n)					
No. of positive cases	15	15	9	10	5
No. of negative cases	0	0	1	0	5
Percentage of positive cells					
Mean $\pm$ SD (%)	27.26 $\pm$ 12.09	20.85 $\pm$ 7.43	9.24 $\pm$ 7.00	20.15 $\pm$ 15.70	2.27 $\pm$ 5.65
% of positive cells (n (%))					
0 = No positive cells	0	0	1 (10)	0	5 (50)
1 = < 10%	2 (13.33)	1 (6.67)	5 (50)	2 (20)	5 (50)
2 = 10–50%	12 (80)	14 (93.33)	4 (40)	8 (80)	0
3 = > 50–80%	1 (6.67)	0	0	0	0
4 = > 80%	0	0	0	0	0
Intensity					
0 = No color	0	0	1 (10)	0	5 (50)
1 = Mild	3 (20)	11 (73.33)	6 (60)	2 (20)	5 (50)
2 = Moderate	9 (60)	4 (26.67)	3 (30)	5 (50)	0
3 = Intense	3 (20)	0	0	3 (30)	0
IRS score					
0–1 = Negative	1 (6.67)	0	6 (60)	2 (20)	10 (100)
2–3 = Mild	3 (20)	11 (73.33)	1 (10)	0	0
4–8 = Moderate	11 (73.33)	4 (26.67)	3 (30)	8 (80)	0
9–12 = Strongly positive	0	0	0	0	0

that of patients with negative nodal metastasis and clinical stage I or II. However, the expression of cathepsin L between well-differentiated OSCC and poorly differentiated OSCC was not statistically significant difference.⁸ In addition, overexpression of cathepsin L mRNA and protein was detected in 35% and 50% of specimens from oral dysplasia patients whose oral lesions had not progressed to OSCC respectively. The percentages of cases with overexpression of cathepsin L mRNA and protein were higher in specimens from patients whose oral lesions had progressed to OSCC with 63% and 67% in that order. The level of cathepsin L was lower in the non-progressive oral dysplasias than that of the oral cancers. Nevertheless, the degree of dysplasia was not related to the level of cathepsin L expression.¹¹ Our study also observed cathepsin L expression in dysplastic and inflammatory cells in connective tissues of oral epithelial dysplasia in 90% of samples. We found only 9.24 $\pm$ 7.00% of positive cells with mild intensity in most of the cases. The reason could be due to the specimens used in this study. They were histopathological categorized as moderate oral epithelial dysplasia (7 cases) and severe oral epithelial dysplasia (3 cases). However, we did not know whether the lesions had a potential to progress to OSCC at the time of biopsy, which seems to be an important factor for cathepsin L overexpression.

In the current study, there was no statistically significant difference in the percentage of positive cathepsin L cells between erosive OLP and non-erosive OLP. The similar expression pattern between 2 groups was also observed. However, most of erosive OLP cases showed moderate staining intensity (60%) and moderate IRS score (73.33%), while most of non-erosive OLP showed mild staining intensity (73.33%) and mild IRS score (73.33%). These results perhaps suggest that the severity of OLP maybe related to the level of cathepsin L. Though the intensity of positive cathepsin L cells between erosive OLP and OSCC were comparable (80% of both groups showed moderate to intense staining), the cathepsin L expression patterns between erosive OLP and OSCC cases were different. The cathepsin L expression in OSCC cases were mostly found in tumor cells and keratin pearls, whereas in erosive OLP, the expression was observed in the cytoplasm of the epithelial cells near basement membrane zone and the inflammatory cells. These results may suggest that the roles of cathepsin L in these two diseases are different.

Although there was no previous reports on the expression of cathepsin L in OLP, the expression of cathepsin L in skin lichen planus have been demonstrated.^{12,13} Cathepsin L was shown to overexpress in skin lichen planus compared to controls.¹² Similar to our current results

on OLP, the cathepsin L expression was found in the cytoplasm of epidermal cells mainly in diffuse staining pattern and in inflammatory cells in skin lichen planus. The various degrees of staining intensity were observed ranging from mild to intense.¹² However, Bylaite and colleague did not find cathepsin L expression in epidermis but in lymphohistocytic infiltrates and endothelial cells of blood vessels of skin lichen planus.¹³ Because cathepsin L plays a role in apoptosis of keratinocytes,^{21,22} we expect that cathepsin L should be expressed in epidermis. The possible explanation for why they did not detect cathepsin L expression in epidermis may be due to the histopathology of skin lichen planus specimens used, and might not represent the basal cell degeneration (data not shown). Taken together, these results suggest the possible role of cathepsin L in pathogenesis of skin lichen planus. Thus, cathepsin L could also contribute to the OLP pathogenesis.

Oral lichen planus is a chronic inflammatory autoimmune disease involving T-cell mediated pathogenesis. The pathogenesis involved activation of keratinocytes and antigen-presenting cells by unidentified antigen(s).²³ Major histocompatibility complex (MHC) class I and MHC class II are contributed to pathogenesis of the disease. In addition, apoptosis is considered one of the mechanisms for basal cell death in OLP.^{23,24} Previous data suggest that cathepsin L plays an essential role in MHC class II antigen presentation²⁵ and in cell death.^{26,27} These evidences indicate the possible role of cathepsin L in OLP pathogenesis.

In conclusion, according to our results, it can be implied that cathepsin L plays a role in pathogenesis of OLP and may be associated with OLP severity. Whether or not cathepsin L plays any roles in cancer transformation in OLP needs more investigation.

Funding

This work was supported by the grant from the Faculty of Dentistry, Srinakharinwirot University no.361/2562.

Declaration of competing interest

The authors declare no conflict of interests.

Acknowledgements

We would like to thank Dr Piamkamon Vacharotayangul for reading the manuscript. We would also like to thank Ms Utamaporn Boonzong

for her help in this study.

References

- McCartan BE, Healy CM. The reported prevalence of oral lichen planus: a review and critique. *J Oral Pathol Med.* 2008;37:447–453.
- Shirasuna K. Oral lichen planus: malignant potential and diagnosis. *Oral Sci Int.* 2014;11:1–7.
- Au J, Patel D, Campbell JH. Oral lichen planus. *Oral Maxillofac Surg Clin.* 2013;25:93–100 (vii).
- Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Thongprasom K. Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;100:164–178.
- Turk V, Stoka V, Vasiljeva O, et al. Cysteine cathepsins: from structure, function and regulation to new frontiers. *Biochim Biophys Acta.* 2012;1824:68–88.
- Olson OC, Joyce JA. Cysteine cathepsin proteases: regulators of cancer progression and therapeutic response. *Nat Rev Canc.* 2015;15:712–729.
- Hsu K-F, Wu C-L, Huang S-C, et al. Cathepsin L mediates resveratrol-induced autophagy and apoptotic cell death in cervical cancer cells. *Autophagy.* 2009;5:451–460.
- Nakashima T, Yasumatsu R, Masuda M, Clayman GL, Komune S. Prognostic value of cathepsin L and its inhibitor headpin in oral squamous cell carcinoma. *J Laryngol Otol.* 2012;126:1134–1137.
- Tamhane T, Llukumbura R, Lu S, Maelandsmo GM, Haugen MH, Brix K. Nuclear cathepsin L activity is required for cell cycle progression of colorectal carcinoma cells. *Biochimie.* 2016;122:208–218.
- Thomssen C, Schmitt M, Goretzki L, et al. Prognostic value of the cysteine proteases cathepsins B and cathepsin L in human breast cancer. *Clin Canc Res.* 1995;1:741.
- Macabeo-Ong M, Shiboski CH, Silverman S, et al. Quantitative analysis of cathepsin L mRNA and protein expression during oral cancer progression. *Oral Oncol.* 2003;39:638–647.
- Ibrahim ZA, El Ashmawy AA, Abd El-Naby NM, Ghoraba HM. Immunohistochemical expression of cathepsin L in atopic dermatitis and lichen planus. *Indian J Dermatol.* 2015;60:13–20.
- Bylaite M, Moussali H, Marciukaitiene I, Ruzicka T, Walz M. Expression of cathepsin L and its inhibitor hurpin in inflammatory and neoplastic skin diseases. *Exp Dermatol.* 2006;15:110–118.
- Remmele W, Stegner HE. [Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue]. *Pathologe.* 1987;8:138–140.
- Giuliani M, Troiano G, Cordaro M, et al. Rate of malignant transformation of oral lichen planus: a systematic review. *Oral Dis.* 2019;25:693–709.
- Georgakopoulou EA, Ahtari MD, Ahtaris M, Foukas PG, Kotsinas A. Oral lichen planus as a preneoplastic inflammatory model. *J Biomed Biotechnol.* 2012;2012:759626.
- Sudhan DR, Siemann DW. Cathepsin L targeting in cancer treatment. *Pharmacol Ther.* 2015;155:105–116.
- Lankelma JM, Voorend DM, Barwari T, et al. Cathepsin L, target in cancer treatment? *Life Sci.* 2010;86:225–233.
- Kawada A, Hara K, Kominami E, Tezuka T, Takahashi M, Takahara H. Precursor of rat epidermal cathepsin L: purification and immunohistochemical localization. *J Dermatol Sci.* 2000;23:36–45.
- Palungwachira P, Kakuta M, Yamazaki M, et al. Immunohistochemical localization of cathepsin L and cystatin A in normal skin and skin tumors. *J Dermatol.* 2002;29:573–579.
- Welss T, Sun J, Irving JA, et al. Hurpin is a selective inhibitor of lysosomal cathepsin L and protects keratinocytes from ultraviolet-induced apoptosis. *Biochemistry.* 2003;42:7381–7389.
- Tobin DJ, Foitzik K, Reinheckel T, et al. The lysosomal protease cathepsin L is an important regulator of keratinocyte and melanocyte differentiation during hair follicle morphogenesis and cycling. *Am J Pathol.* 2002;160:1807–1821.
- Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med.* 2002;13:350–365.
- Gupta S, Jawanda MK. Oral lichen planus: an update on etiology, pathogenesis, clinical presentation, diagnosis and management. *Indian J Dermatol.* 2015;60:222–229.
- Hsing LC, Rudensky AY. The lysosomal cysteine proteases in MHC class II antigen presentation. *Immunol Rev.* 2005;207:229–241.
- Chwieralski CE, Welte T, Buhling F. Cathepsin-regulated apoptosis. *Apoptosis.* 2006;11:143–149.
- Mrschik M, Ryan KM. Lysosomal proteins in cell death and autophagy. *FEBS J.* 2015;282:1858–1870.