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Original Article

Matrix metalloproteinase-9 upregulation in keratinocytes of oral lichen planus via c-Jun N-terminal kinase signaling pathway activation

Xinke Jiang [a,b], Yiwen Deng [a,b], Yirao Lai [a,b], Guanhuan Du [a,b], Xiye Li [a,b], Xiaojie Yang [a,b], Mingya Li [c], Lei Sun [c], Yufeng Wang [a,b*], Guoyao Tang [a,b,d**]

[a] *Department of Oral Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[b] *College of Stomatology, Shanghai Jiao Tong University, National Center for Stomatology, National Clinical Research Center for Oral Diseases, Shanghai Key Laboratory of Stomatology, Shanghai, China*
[c] *Institute of Developmental Biology and Molecular Medicine, Fudan University, Shanghai, China*
[d] *Department of Stomatology, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

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Abstract *Background/purpose:* Oral lichen planus (OLP) is a chronic inflammatory disorder characterized by basement membrane disruption, which plays a crucial role in its pathogenesis. Matrix metalloproteinases (MMPs), a group of proteolytic enzymes, contribute to the degradation of the basement membrane. The specific MMPs secreted by keratinocytes in OLP lesions and relevant regulatory mechanisms are not fully understood. This study aimed to investigate the involvement of MMPs in OLP pathogenesis, focusing on their expression in keratinocytes and regulatory mechanisms.
Materials and methods: MMP mRNA expression in OLP epithelium was analyzed using RNA sequencing data obtained from the Gene Expression Omnibus (GEO) database. Mucosa samples from 30 OLP patients and 30 healthy controls were collected to observe the expression and regulation of MMPs in keratinocytes. The involvement of the mitogen-activated protein kinase (MAPK) pathway in MMP regulation was studied using HaCaT cells.

* Corresponding author. Department of Oral Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 639 Zhizaoju Road, Huangpu District, Shanghai, 200011, China.
** Corresponding author. Department of Stomatology, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Yangpu District, Shanghai, 200092, China.
E-mail addresses: wangyf1701@sjtu.edu.cn (Y. Wang), tanggy@shsmu.edu.cn (G. Tang).

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Results: RNA sequencing analysis revealed upregulation of *MMP1* and *MMP9* in OLP epithelium. MMP9 expression was predominantly observed in basal keratinocytes of OLP lesions. Elevated levels of phosphorylated c-Jun N-terminal kinase (JNK), a component of the MAPK pathway, were detected in OLP samples and co-localized with MMP9 in keratinocytes. Activation of the JNK pathway in HaCaT cells induced MMP9 expression, implicating JNK signaling in MMP9 regulation.
Conclusion: Keratinocytes contribute to OLP pathogenesis by secreting MMP9 through JNK pathway activation. This understanding may provide insights into targeted therapeutic interventions for this chronic recurrent disease.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disorder of oral mucosa affecting approximately 1.01% (0.49%–1.43%) of the global population.[1] As the most common clinical form, reticular OLP presents with a pattern of white lesions on the oral mucosa. As the disease severity increases, erosive and ulcerative lesions caused by the thinning or complete loss of the epithelium are observed. OLP is characterized histologically by a dense subepithelial lymphocytic infiltration, degeneration of basal keratinocytes and basement membrane disruption, posing significant challenges due to its recurrence and potential malignant transformation.[2,3] The integrity of the basement membrane is important to maintain oral mucosal homeostasis.[4,5] Nevertheless, the pathogenic mechanisms underlying the proteolytic degradation of the basement membrane in OLP remain incompletely understood, hindering the development of targeted therapies.

As a large family of zinc-dependent endopeptidases, matrix metalloproteinases (MMPs) participate in various proteolytic events.[6,7] They play significant roles in tissue remodeling, angiogenesis and immune response modulation. In pathological conditions, dysregulated MMP activity may contribute to chronic inflammation, fibrosis, tissue breakdown, and invasion and metastasis of cancer.[8–10] MMPs are capable of digesting components of basement membrane, a specialized extracellular matrix structure that separates epithelium and underlying connective tissue. Basement membrane disruption by MMPs is associated with heightened tissue permeability and inflammation.[7,9]

It has been recognized that the MMP levels increase when mast cells, T cells, and macrophages accumulate and activate in OLP lesions.[2,11] The increased proteolytic activity then leads to basement membrane destruction and detachment of keratinocytes from the basement membrane in OLP.[2,12] Despite being the most abundant cell type in mucosal epithelium, keratinocytes were viewed as passive recipients of immune cell function.[13,14] In the past decade, emerging evidence has shown that keratinocytes could be the an innate player in the onset and progression of OLP.[2,15,16] Several MMPs have been detected in the epithelial region of OLP, indicating that pathologically activated keratinocytes in OLP may secret MMPs that disrupt the basement membrane.[17–19] Moreover, Jang et al.[20] reported that in human epidermal keratinocytes, the expression of MMP1 and MMP3 are suppressed via the downregulation of the mitogen-activated protein kinase (MAPK) pathway. Seomun et al.[21] reported that in TGFβ1-induced HaCaT cells (immortalized human skin keratinocytes), MMPs expression is regulated via MAPK signaling. The MAPK pathway plays a crucial role in the extracellular matrix remodeling, and involves extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun N-terminal kinase (JNK, also known as SAPK).[22] These observations indicate the potential participation of MAPKs in regulation of MMPs secretion in oral mucosal keratinocytes. However, the specific MMPs secreted by keratinocytes in OLP lesions and relevant regulatory mechanisms are not fully understood. We hypothesized that the MAPK pathway regulates the secretion of specific MMPs by keratinocytes in OLP lesions, contributing to basement membrane disruption. To test this, we examined which MMPs were secreted by keratinocytes in OLP lesions and whether this process was the MAPK pathway-dependent.

Materials and methods

Data acquisition, processing and analysis

RNA sequencing and microarray data were searched through the Gene Expression Omnibus (GEO) database and filtered based on the keywords "oral lichen planus" and "homo sapiens." Included datasets met the following criteria: ≥6 samples available for analysis; samples from patients diagnosed with "oral lichen planus"; and healthy samples as controls. Raw data and relevant clinical information were extracted and processed in R (RStudio, version 2023.09.1 + 494). Principal component analysis (PCA) was performed to identify outlier samples and reduce unwanted variability. Differentially expressed genes (DEGs) were identified using the "Deseq2" package or the "limma" package for the raw count data or the microarray data, respectively. Gene expression values were normalized and visualized using a heatmap.

Cell culture

HaCaT cells, a human epidermal keratinocyte cell line, were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 15% fetal bovine serum (FBS) and Pen-Strep (100 μg/mL penicillin and 100U/mL streptomycin). All

reagents were purchased from Thermo Fisher Scientific (Waltham, MA, USA). The cell line was authenticated via short tandem repeat sequence analysis, and maintained in a cell culture incubator (Thermo Fisher Scientific) at 37 °C with 5% CO_2. Anisomycin (MedChemExpress, Monmouth Junction, NJ, USA) was dissolved in DMSO at a concentration of 20 mM as a stock solution and stored at −20 °C. SP600125 (MedChemExpress) was dissolved in DMSO at a concentration of 5 mM as a stock solution and stored at −20 °C.

Human mucosa sample collection

This study was performed following the principles of the Helsinki Declaration and was approved by the ethics committee of the Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine (No. SH9H-2021-T100-2). All patients were referred to the Department of Oral Medicine, Shanghai Ninth People's Hospital, China from September 2023 to March 2024. The OLP patients (n = 30) were diagnosed according to the modified WHO criteria,[23] and tissue samples were obtained by punch biopsies of the lesional buccal mucosa. Healthy controls comprised age- and sex-matched individuals (n = 30) undergoing resection of buccal papilloma or fibroma, and tissue samples were obtained during surgical wound trimming. All biopsy procedures were conducted by experienced surgeons, and informed consent was obtained from every patient.

Immunoblotting

Cells and tissue were lysed in RIPA lysis buffer (Beyotime, Shanghai, China) supplemented with protease and phosphatase inhibitors (Beyotime) by low-temperature grinder (Wonbio, Shanghai, China) at 4 °C. The lysates were incubated on ice for 20min and then cleared by high-speed centrifugation (12000 rpm, 15min) at 4 °C. After saving 5% of the supernatants for the BCA assay, the rest underwent denaturation with SDS-PAGE sample loading buffer and were then subjected to Western blotting analysis. Sources and dilutions of primary antibodies were as follows: phospho-SAPK/JNK (Thr183/Tyr185) (#9251, 1:1000; Cell Signaling Technology, Danvers, MA, USA), SAPK/JNK (#9252, 1:1000; Cell Signaling Technology), phospho-ERK1/2 (Thr202/Tyr204) (#4370, 1:1000; Cell Signaling Technology), ERK1/2 (#4695, 1:1000; Cell Signaling Technology), phospho-p38 MAPK (Thr180/Tyr182) (#4511, 1:1000; Cell Signaling Technology), p38 MAPK (#9212, 1:1000; Cell Signaling Technology), MMP9 (N-terminal) (10375-2-AP, 1:1000; Proteintech, Wuhan, China), β-Actin (AC026, 1:20000; Abclonal, Wuhan, China). Protein bands were visualized using an e-Blot touch imager (e-Blot, Shanghai, China). The intensity of each band was quantified and normalized using β-actin as an internal loading control by ImageJ (version 1.54f; NIH, Bethesda, MD, USA).

Immunofluorescence microscopy

For tissue samples, 4% paraformaldehyde-fixed tissues were embedded in paraffin and cut at 3 μm thickness. Following the instructions of the TSA-based multiplex immunohistochemistry/immunofluorescence (mIHC/IF) staining kit (Yuanxi, Shanghai, China), the sections underwent deparaffinization, antigen retrieval, permeabilization, blocking, and incubation with primary antibodies, secondary antibodies labeled with HRP and tyramide-conjugated fluorophores. For cell samples, cells were plated on 24-well glass slides and fixed with 4% paraformaldehyde. Then the slides underwent permeabilization, blocking, and incubation with primary antibodies and fluorophore-conjugated secondary antibodies. Sources and dilutions of primary antibodies were as follows: phospho-SAPK/JNK (Thr183/Tyr185) (#9251, 1:2000; Cell Signaling Technology), phospho-ERK1/2 (Thr202/Tyr204) (#4370, 1:3000; Cell Signaling Technology), phospho-p38 MAPK (Thr180/Tyr182) (#4511, 1:5000; Cell Signaling Technology), MMP1 (CY5330, 1:5000; Abways, Shanghai, China), MMP9 (N-terminal) (10375-2-AP, 1:10000 for tissue samples/1:1000 for cell samples; Proteintech), Cytokeratin 4 (ab51599, 1:5000; Abcam, Cambridge, UK), Cytokeratin 14 (ab7800, 1:20000; Abcam). Sections and slides were mounted in antifade reagent (Beyotime) and imaged by confocal microscopy on a Zeiss LSM 700 instrument (Carl ZEISS, Jena, Germany). The fluorescence images were merged and analyzed using Zeiss ZEN (version 3.8; Carl ZEISS).

Statistical analysis

Statistical analyses were conducted using GraphPad Prism (version 8; GraphPad Software, Boston, MA, USA). Differences between groups were calculated using the Student's *t*-test or one-way ANOVA. A *P*-value of <0.05 was considered significant in all statistical tests.

Results

MMP1 and MMP9 are potentially up regulated in the OLP epithelium

We obtained two datasets (GSE131567 and GSE52130) that met inclusion criteria from the GEO database (Fig. 1A). We conducted PCA analysis for included datasets to remove outlier samples, and the PCA plots (Fig. 1B and C) depict the distribution of samples after removal, with each point representing an individual sample.

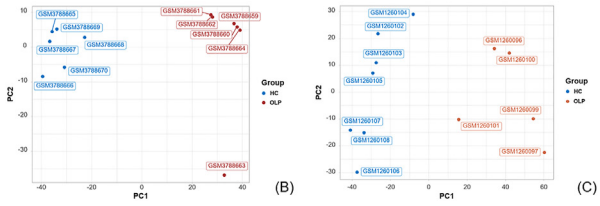
We analyzed the gene expression profiles in oral mucosa samples (GSE131567) and oral mucosal epithelium samples (GSE52130) and used heatmaps to depict the expression pattern of *MMP* families (Fig. 1D and E). We identified the differentially expressed genes and intersected the results (Fig. 1F). *MMP1*, *MMP9*, *MMP10*, *MMP12* were up regulated in both datasets. We searched the normalized single cell RNA levels of the selected genes expressed in the "basal keratinocytes" and "suprabasal keratinocytes" cell types from the Human Protein Atlas database. We included *MMP1* and *MMP9* for further analysis, as the RNA levels of *MMP10* and *MMP12* were less than 1 nTPM in both single cell types.

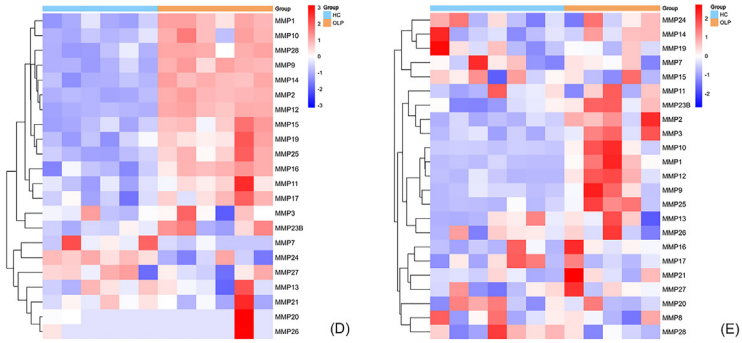
MMP9 expression is upregulated in OLP keratinocytes

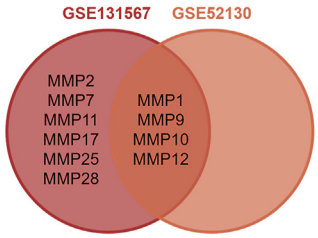
To test our hypothesis that keratinocytes serve as a source of MMP1 and MMP9 in OLP, we examined the expression of

GEO accession	Sample	Expression profiling type	OLP/HC
GSE131567	Oral mucosa	High throughput sequencing	6/6
GSE52130	Oral mucosa epithelium	Array	5/7

(A)







(F)

Figure 1 Analysis of gene expressions of matrix metalloproteinase (MMP) family and intersection of differentially expressed genes (DEGs). (A) Information of the two datasets obtained from Gene Expression Omnibus (GEO) database. (B and C) Principal component analysis (PCA) after removing outlier samples. (D and E) Heatmaps representing gene expression differences of *MMP* family in oral lichen planus (OLP) group and healthy control (HC) group. (F) Venn diagram representing intersection of DEGs from two datasets based on a |Log2FoldChange| $\geq$1.5 and a *P*-value of $<$0.05.

MMP1 and MMP9 under both normal and diseased conditions (Fig. 2A). Consistent with previous reports, we observed MMP1 and MMP9 were expressed and localized mainly in the lymphocytic cell infiltration area of the lamina propria. We also observed prominent expression and distribution of MMP9 within the OLP epithelium. To confirm the expression of MMP9 in keratinocytes, we co-stained MMP9 with Keratin-14 and Keratin-4, markers for basal and suprabasal keratinocytes of buccal mucosa respectively. The expression of MMP9 was seen in epithelial keratinocytes, particularly in the basal layer of rete pegs (Fig. 2B).

JNK is activated by phosphorylation and co-localizes with MMP9 in OLP keratinocytes

We examined the phosphorylation levels of p38 MAPK, ERK, and JNK under both normal and diseased conditions, to test whether MMP9 expression is regulated by the MAPK pathway in OLP. We observed the levels of phosphorylated JNK (pJNK) were obviously augmented in OLP samples, while the levels of phosphorylated p38 MAPK(p-p38) and phosphorylated ERK (pERK) were not altered (Fig. 3A). We furthermore performed co-staining for pJNK, p-p38, and pERK and observed an augmented presence of pJNK within epithelial keratinocytes (Fig. 3B).

MMP9 expression is mediated through activation of the JNK pathway

To explore the potential relationship between pJNK and MMP9, we co-stained the two proteins and observed that in epithelial keratinocytes, phosphorylated JNK was co-localized with MMP9 (Fig. 4A). To determine whether the phosphorylation of JNK regulates the expression of MMP9, we assessed the MMP9 expression level in response to the JNK pathway activation in HaCaT cells. The phosphorylation of JNK is absent in HaCaT cells, thus we utilized Anisomycin as a JNK activator (Fig. S1) and utilized SP600123 as a JNK inhibitor to serve as a negative control. In the presence of Anisomycin treatment, the expression of MMP9 significantly increased after 24 h, and exhibited a time-dependent increase at 24 and 48 h (Fig. 4B and C).

Discussion

OLP is a chronic inflammatory disease that affects the oral mucosa, causing discomfort and potentially leading to malignant transformations.[24,25] Despite extensive research, the precise mechanisms underlying the pathogenesis of lesional keratinocytes remain elusive, hindering the development of effective targeted therapies. In this study, we investigated the specific MMPs secreted by keratinocytes in OLP lesions and focused particularly on MMP9. We also explored the regulatory role of the MAPK pathway, specifically JNK activation, in MMP9 expression of keratinocytes.

The pathogenesis of OLP involves the interplay between keratinocytes, immune cells, and other skin-resident cells. In previous studies, the basement membrane disruption has been considered as an immune cell-driven process, which contributes to the degeneration of keratinocytes.[2,12,26] Increasing attention has been raised to lesional keratinocytes which may play a vital part in the onset and progression of OLP, while few research focused on whether keratinocytes have an influence on the homeostasis of basement membrane. The basement membrane disruption is commonly facilitated by MMP activation.[12] As crucial mediators of tissue remodeling, elevated levels of MMPs,

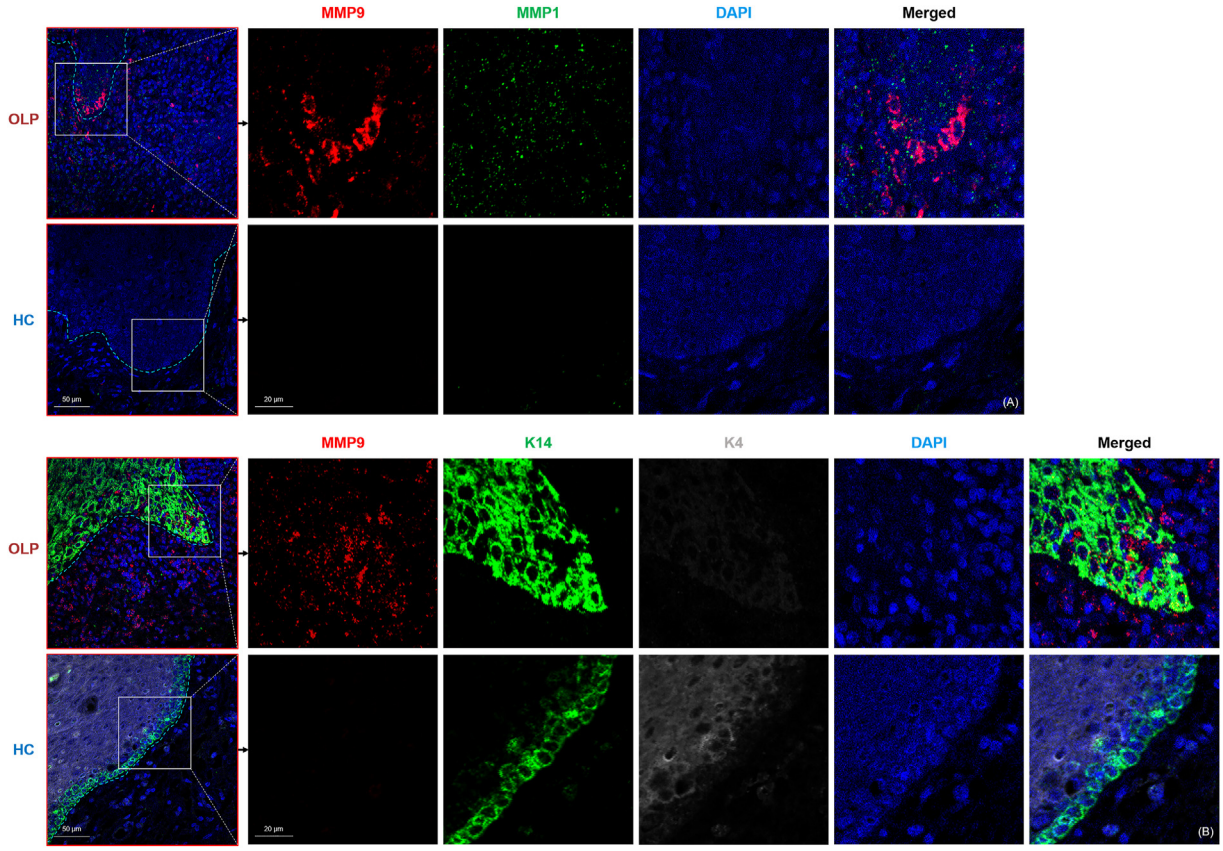


Figure 2 Multiplex immunohistochemistry/immunofluorescence (mIHC/IF) staining in oral mucosa tissue. (A) Representative confocal microscopy images stained for MMP9 (red), and MMP1 (green). (B) Representative confocal microscopy images stained for MMP9 (red), Keratin-14 (K14, green) and K4 (grey). Cell nuclei were counterstained with DAPI (blue). Skyblue dashlines indicates basement membrane, and white boxes indicate enlarged regions.

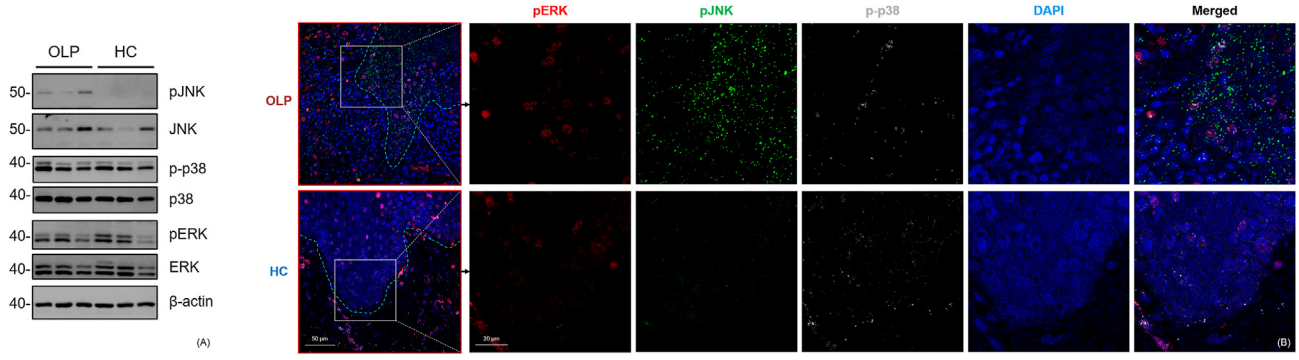


Figure 3 Western blot analysis and mIHC/IF staining in oral mucosa tissue. (A) Representative western blot images showing the phosphorylation status of protein JNK, p38 and ERK (pJNK, p-p38 and pERK) in oral mucosa tissue. Total protein JNK, p38 and ERK and β-actin as a loading control were also detected. (B) Representative confocal microscopy images stained for pERK (red), pJNK (green) and p-p38 (grey). Cell nuclei were counterstained with DAPI (blue). Skyblue dashlines indicates basement membrane, and white boxes indicate enlarged regions.

including MMP1, 2, 3, 7, and 9, have been detected in OLP lesions.[17–19] Several MMPs have been detected in the epithelial region of OLP, yet it is still obscure which MMPs keratinocytes in the OLP lesion secret. Our analysis of RNA sequencing data from oral mucosal samples revealed a potential upregulation of MMP1 and MMP9 in OLP epithelium, suggesting their involvement in the pathogenesis of the disease. Interestingly, MMP9 showed prominent expression within the OLP epithelium, indicating a potential role of keratinocytes in MMP9 secretion.

MMP9, also known as Gelatinase B, is a key gelatinase in both normal and pathological inflammatory processes.[7,9] MMP9 plays a crucial role in regulating the composition of the extracellular matrix and can cleave various types of

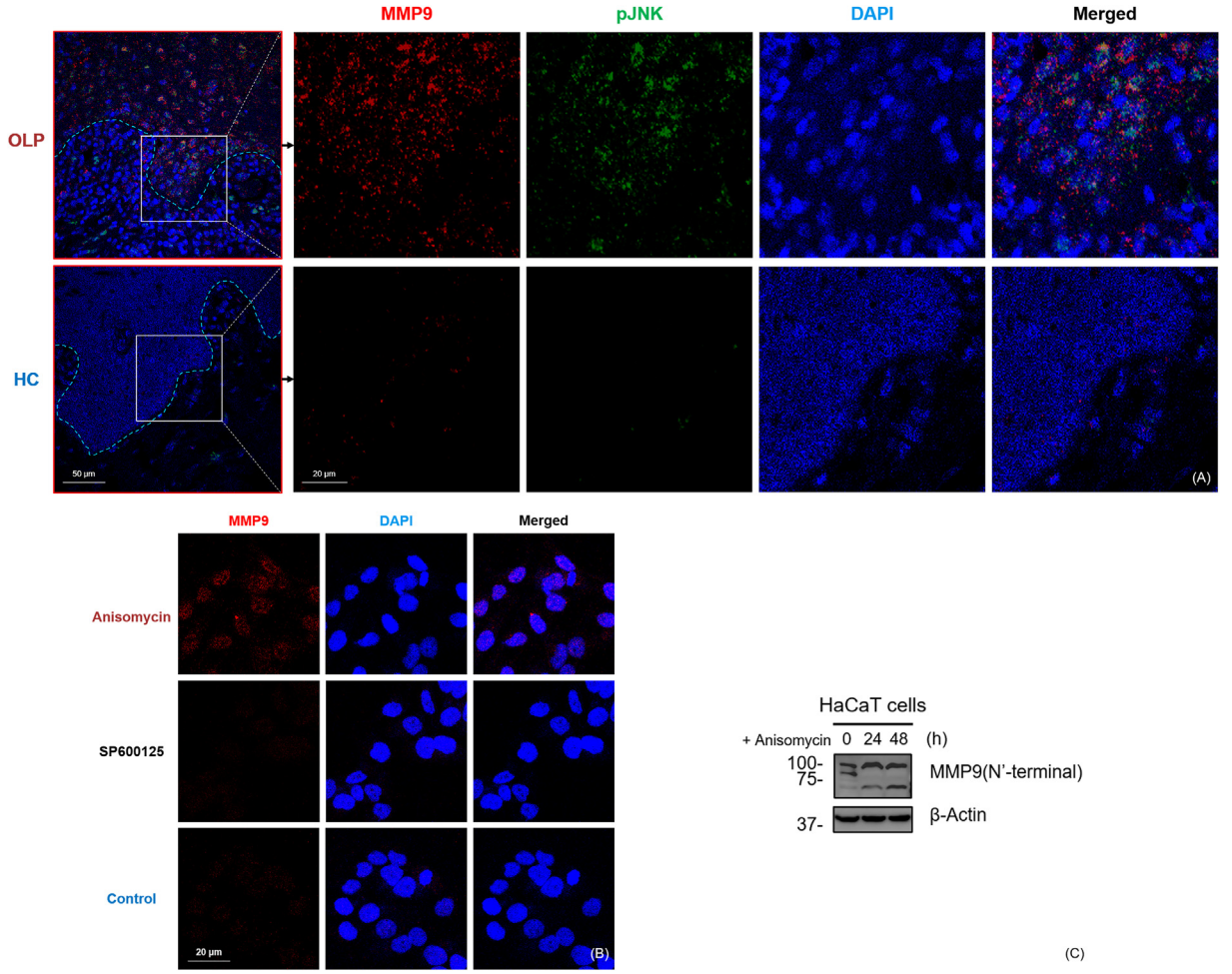


Figure 4 Western blot analysis and mIHC/IF staining in oral mucosa tissue and HaCaT cells. (A) Representative confocal microscopy images stained for MMP9 (red), pJNK (green). Cell nuclei were counterstained with DAPI (blue). Slyblue dashlines indicates basement membrane, and white boxes indicate enlarged regions. (B) Representative confocal microscopy images stained for MMP9 (red) in HaCaT cell line after treatment with 1 μM Anisomycin dissolved in DMSO, 1 μM SP600125 dissolved in DMSO or DMSO control for 24 h. Cell nuclei were counterstained with DAPI (blue). (C) Representative western blot images showing the levels of MMP9 in HaCaT cell line. Cells were treated with 1 μM Anisomycin dissolved in DMSO or DMSO control for the indicated time points (0, 24 and 48 h). Protein β-actin as a loading control were also detected.

collagens, including type 4 collagen which is the major component of the basement membrane.[7] The increased expression and secretion of MMP9 in OLP lesions contribute to the degradation of basement membrane, resulting in the epithelial infiltration of lymphocytes and the degeneration of basal cells.[2,19] It is recognized that MMP9 is secreted by macrophages and detected in neutrophil cytoplasm.[27] Studies of OLP pathology have shown MMP9 is also produced by T cells at lesional sites.[2,19] Additionally, Wang et al.[28] reported elevated MMP9 levels induced by IL9 in OLP Th9 cells. Conflicting opinions have been reported about the relationship between OLP lesional keratinocytes and the distribution of MMP9. Zhou et al.[29] reported that MMP9 was associated with OLP lesional T cells but not epithelial cells, while Paulusová et al.[19] found the expression of MMP9 both in the lamina propria and in the epithelium in all cases of OLP. Obviously, the distribution of MMP9 in OLP epithelium and the relevant mechanism still remain unclear. In our study, the expression of MMP9 was co-stained with keratins in OLP samples, and we identified that OLP lesional keratinocytes expressed and secreted MMP9. Furthermore, we noticed more significant expression of MMP9 in the basal layer of rete pegs than in other regions of epithelium, indicating that MMP9 may play an important part in aggravating the disease severity as rete pegs are important for providing structural support and enhancing adherence of epithelium and lamina propria.

MAPKs are serine-threonine kinases that mediate a variety of cellular activities and play a crucial role in the extracellular matrix remodeling.[22,30] Our investigation revealed an activation of the JNK pathway and a potential regulatory relationship between JNK activation and MMP9 expression in OLP keratinocytes. To establish causality, we activated the JNK pathway in HaCaT cells, and observed a significant increase in MMP9 expression in response to JNK activation, supporting the notion that the JNK pathway regulates MMP9 expression in keratinocytes. Furthermore, it has reported that the JNK and p38 MAPK signaling

pathways can be activated by proinflammatory cytokines such as tumor necrosis factor-α (TNFα) and interleukin-1β (IL1β),[31,32] and keratinocytes from OLP lesions have been reported to produce increased TNFα and IL1β than from healthy oral mucosa.[2] In addition, the PI3K/Akt/NF-κB pathway has also been implicated in regulating MMP9 expression,[33] although no significant activation was observed in OLP samples based on our unpublished data (Fig. S2). Further researches could focus on whether these proinflammatory cytokines lead to MMP9 expression via the JNK pathway in lesional keratinocytes, helping elucidate the molecular mechanisms underlying OLP pathogenesis.

In conclusion, our study provides novel insights into the involvement of keratinocytes in the pathogenesis of OLP. We have demonstrated that MMP9 expression is elevated in lesional keratinocytes driven by activation of the JNK pathway, which supports our hypothesis and suggests potential therapeutic targets from the perspective of keratinocyte-mediated mechanisms.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2024.07.010.

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