Int. J. Morphol.,
44(2):625-631, 2026.

PLAP-1/Asporin Gets Involved in Histological Alterations of External Root Surface Following Human Severe Periodontitis

La PLAP-1/Asporina Participa en las Alteraciones Histológicas de la Superficie Radicular Externa Después de Periodontitis Grave en Humanos

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PAN, K.; LI, Z.; YI, X.; JIN, C.; ZHU, M.; YU, X. & XIAO, C. PLAP-1/asporin gets involved in histological alterations of external root surface following human severe periodontitis. *Int. J. Morphol., 44(2)*:625-631, 2026.

SUMMARY: PLAP-1/asporin is a key regulator in the maintenance of periodontal homeostasis. However, the involvement of PLAP-1/asporin in histological alterations of the external root surface following severe human periodontitis remains poorly reported. In this study, the external root surface was observed in human periodontitis cases, and the role of PLAP-1/asporin in this pathological process was also investigated. Inflammatory infiltration, periodontal tissue necrosis, and resorption of cementum (and even dentin) were observed on the external root surface of teeth affected by severe periodontitis. Additionally, inflammatory cells and multiple clastic cells were detected around sites of external inflammatory resorption in cases of severe human periodontitis. Notably, the expression of PLAP-1/asporin in inflammatory tissues was significantly higher than that in normal periodontal ligaments. Positive PLAP-1/asporin expression was also identified in CD68-positive infiltrating inflammatory cells and multiple clastic cells (which are responsible for resorbing mineralized tissues). Collectively, this study correlates pathological alterations of the external root surface with severe periodontitis, and demonstrates that PLAP-1/asporin is involved in histological alterations of the external root surface following severe human periodontitis.

KEY WORDS: Periodontal ligament-associated protein-1; Asporin; Periodontitis; External resorption.

INTRODUCTION

Periodontitis is regarded as one of the most common human diseases, exerting a significant impact on patients' oral function and oral health-related quality of life (Dannewitz *et al*., 2021; Dibello *et al*., 2024; Duque Duque *et al*., 2024). Currently, numerous studies focus on the pathological loss of the periodontal ligament (PDL) and alveolar bone in periodontitis. However, pathological alterations of the external root surface in periodontitis have been rarely reported.

Investigating the interrelationship between primary periodontal lesions and secondary endodontic lesions is of great significance, as it provides biological evidence for the etiology, diagnosis, prognosis, and treatment of combined periodontal-endodontic lesions (Rotstein, 2017; Kuzekanani & Mollamohamadi Kermani, 2024). Previous studies have shown that periodontal bacteria and/or their endotoxins in patients with severe chronic periodontitis have the potential to induce pathological changes in the dental pulp via lateral or accessory canals (Yu *et al*., 2020; Fang *et al*., 2021). If damage to the external root surface leads to the exposure of dentinal tubules (Abbott & Lin, 2022), bacteria in the PDL and/or their endotoxins can also easily migrate through these dentinal tubules to reach the root canal system (Rotstein & Simon, 2004). In periodontitis, infected PDL not only induces the resorption of adjacent alveolar bone by osteoclasts but also triggers inflammatory resorption within the root by

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Kexu Pan, Zhuoyang Li and Xinxuan Yi cntributed equally.
FUNDING . Jinan Municipal Science and Technology Plan Project, Grant/Award Numbers: 202328024, 202430029; Science and Technology Development Program of Jinan Municipal Health Commission, Grant/Award Numbers: 2023-1-63, 2025305009.

Received: 2025-12-13 Accepted: 2026-02-13

activating clastic cells. Nevertheless, histological alterations of the external root surface in patients with severe human periodontitis remain poorly reported. Understanding the histological alterations and pathogenic mechanism of external root surface resorption is crucial for its prevention and treatment (Abbott & Lin, 2022).

Asporin, also known as periodontal ligament-associated protein-1 (PLAP-1), is a proteoglycan that is preferentially and highly expressed in the PDL (Yamada *et al*., 2001; Manohar *et al*., 2024). PLAP-1/asporin plays important roles in the cytodifferentiation and mineralization of PDL cells, as well as in the maintenance of periodontal tissue homeostasis (Kinoshita *et al*., 2023; Zhou *et al*., 2023; Liu *et al*., 2024). Specifically, PLAP-1/asporin inhibits bone morphogenetic protein 2 (BMP-2)-induced differentiation of PDL cells (Yu *et al*., 2019). PLAP-1 also positively correlates with receptor activator of nuclear factor kappa-B ligand (RANKL) and CD68+ osteoclasts during the development of the osseous eruption canal (Yamaba *et al*., 2015).

Scholars have also conducted research to explore the role of PLAP-1/asporin in periodontitis (Yamaba *et al*., 2015). PLAP-1-positive inflammatory cells contribute to periodontal inflammation and alveolar bone loss in a rat model of experimental periodontitis (Chen *et al*., 2023). However, the involvement of PLAP-1/asporin in histological alterations of the external root surface in patients with severe human periodontitis remains poorly documented.

In this study, the external root surface of teeth from patients with severe chronic periodontitis was observed. Additionally, the expression and distribution of PLAP-1/asporin were investigated using immunofluorescence and double-labeled immunofluorescence. The expression of PLAP-1/asporin in the PDL was also analyzed via western blotting.

MATERIAL AND METHOD

Samples and Tissue preparation. Twenty teeth extracted due to severe chronic periodontitis were selected for this study. Severe chronic periodontitis was diagnosed in accordance with the criteria defined by the American Academy of Periodontology (AAP). This study was approved by the Ethics Committee of Jinan Stomatological Hospital (JNSKQYY-2023-019), and all patients provided written informed consent voluntarily prior to participation. After extraction, the teeth were fixed in 4 % paraformaldehyde for 48 h and subsequently demineralized in 15 % ethylenediaminetetraacetic acid (EDTA) for 6 months. Serial 5-μm paraffin sections were prepared for hematoxylin and eosin (HE) staining and immuno fluorescence analysis.

Hematoxylin and Eosin (HE) Staining. Paraffin sections were first deparaffinized with xylene (two changes, 10 minutes each) and then rehydrated through a graded ethanol series (100 %, 95 %, 80 %, and 70 % ethanol, 5 min each). Sections were stained with hematoxylin solution for 3 min to visualize cell nuclei, followed by rinsing with running tap water for 5 min to remove excess stain. Finally, sections were counterstained with eosin solution for 30 s, dehydrated through a reversed ethanol series, cleared with xylene, and mounted with neutral balsam for microscopic observation.

Immunofluorescence and Double-Labeled Immuno fluorescence. Paraffin sections were deparaffinized in xylene (two changes, 10 min each) and rehydrated via a graded ethanol series. For antigen retrieval, sections were immersed in citrate buffer (pH 6.0) and heated in a microwave for 15 min, then cooled to room temperature naturally. After blocking with 5 % bovine serum albumin (BSA) in phosphate-buffered saline (PBS) for 1 h at 37 °C to prevent non-specific binding, sections were incubated with a polyclonal antibody against asporin (dilution 1:200, Invitrogen, USA) overnight at 4°C. The next day, sections were rinsed with PBS (three times, 5 min each) and incubated with the secondary antibody—rhodamine (TRITC)-conjugated goat anti-rabbit IgG (dilution 1:300, Abcam)—for 1 hat 37 °C in the dark.

For double-labeled immunofluorescence, sections were processed with the same antigen retrieval and blocking steps as described above. They were then co-incubated with two primary antibodies overnight at 4 °C: mouse anti-CD68 (dilution 1:100, Abcam) and rabbit anti-asporin (dilution 1:200, Invitrogen). After rinsing with PBS (three times, 5 min each), sections were incubated with a mixture of secondary antibodies—fluorescein isothiocyanate (FITC)-conjugated goat anti-mouse IgG (dilution 1:300, Abcam) and cyanine 3 (CY3)-conjugated goat anti-rabbit IgG (dilution 1:300, Abcam)—for 1 hour at 37 °C in the dark. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI) solution (dilution 1:1000) for 5 min at room temperature. All stained sections were rinsed with PBS, mounted with anti-fade mounting medium, and observed under a laser scanning confocal microscope.

Western Blotting Analysis. Total proteins were extracted from periodontal ligament tissues using the Minute™ Total Protein Extraction Kit for Animal Cultured Cells and Tissues (Inventbiotech, Minneapolis, MN, USA), following the manufacturer's instructions. Equal amounts of protein were separated by 10 % sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and then electro transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Membranes

were blocked with 5 % non-fat milk in Tris-buffered saline with Tween 20 (TBST) for 1 hour at room temperature, then incubated overnight at 4°C with primary antibodies against asporin (dilution 1:500, Abcam) and b-actin (dilution 1:500, Abcam; used as an internal reference). Horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG (dilution 1:10,000, CWBiotech, Beijing, China) for 1 hour at room temperature. Protein bands were visualized using an Amersham Imager 800 (Cytiva, Marlborough, MA, USA), and band intensities were quantified using ImageJ software.

Statistical Analysis. All experimental data are presented as the mean ± standard deviation (SD) from at least three independent experiments. Statistical comparisons were performed using Student's t-test with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

Histological Observation of the External Root Surface in Human Severe Periodontitis

Based on histological analysis of twenty teeth extracted from patients with severe chronic periodontitis, only a small amount of periodontal ligament (PDL) tissue remained attached to the external root surface post-extraction. In the residual PDL, varying degrees of inflammatory infiltration, tissue degeneration, and necrosis were observed (Figs. 1A,B,C).

In most cases of severe human periodontitis, large areas of the cementum surface remained intact; however, external inflammatory resorption was detected in some specimens. At sites of external inflammatory resorption, resorption of cementum (and in some instances, dentin) was observed, accompanied by the presence of inflammatory cells and multiple clastic cells (Figs. 2A,B).

Increased Expression of PLAP-1/Asporin in the PDL Tissues of Human Periodontitis

Immunofluorescence staining results demonstrated the expression of PLAP-1 in the PDL of teeth with severe chronic periodontitis (Figs. 3A-C). Western Blotting analysis further revealed that the expression level of PLAP-1/asporin in the PDL tissues of periodontitis patients was significantly higher than that in normal PDL tissues. This finding suggests that PLAP-1/asporin may be involved in the progression of periodontal inflammation (Fig. 3D).

Involvement of PLAP-1/Asporin in Inflammatory Infiltration and External Inflammatory Resorption in Human Severe Periodontitis.

A large number of inflammatory infiltrating cells were observed in the PDL of teeth with severe chronic periodontitis. Immunofluorescence co-localization analysis showed that PLAP-1/asporin-positive signals were co-localized with CD68-positive infiltrating inflammatory cells, indicating that PLAP-1/asporin is expressed in these inflammatory cells (Fig. 4).

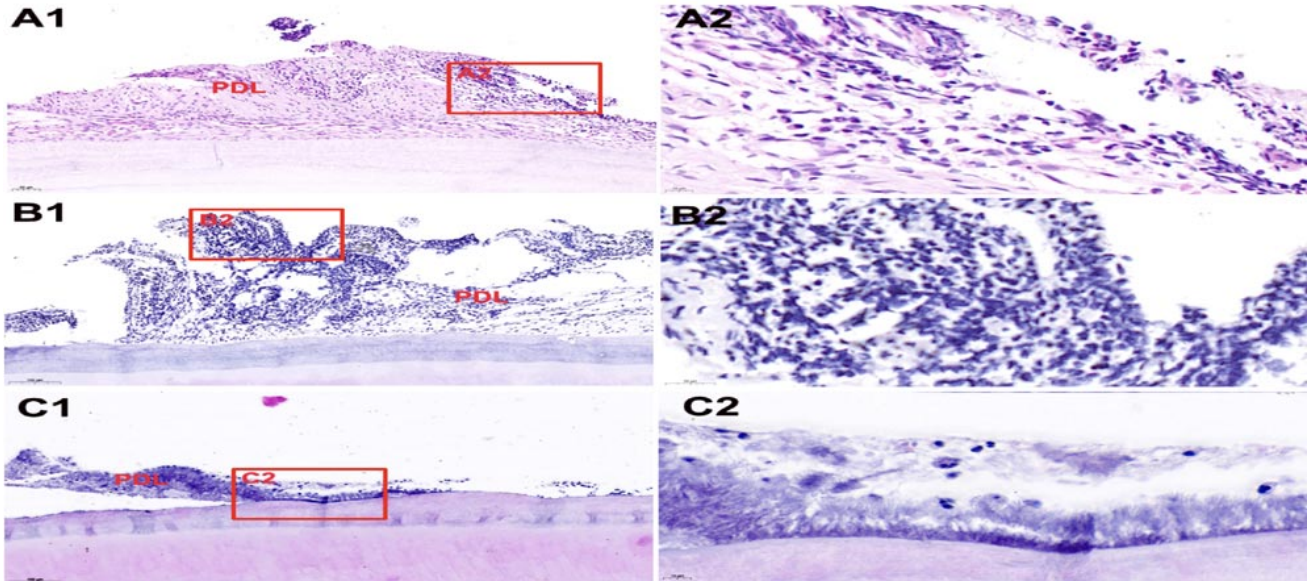

Fig. 1. Histological observation of the external root surface in human severe periodontitis. Only a few periodontal ligament tissues remained attached to the external root surface after tooth extraction in human severe periodontitis. Mild inflammatory infiltration (A1 and A2), severe inflammatory infiltration (B1 and B2), even tissue degeneration and necrosis (C1 and C2) occurred in the periodontal ligaments.

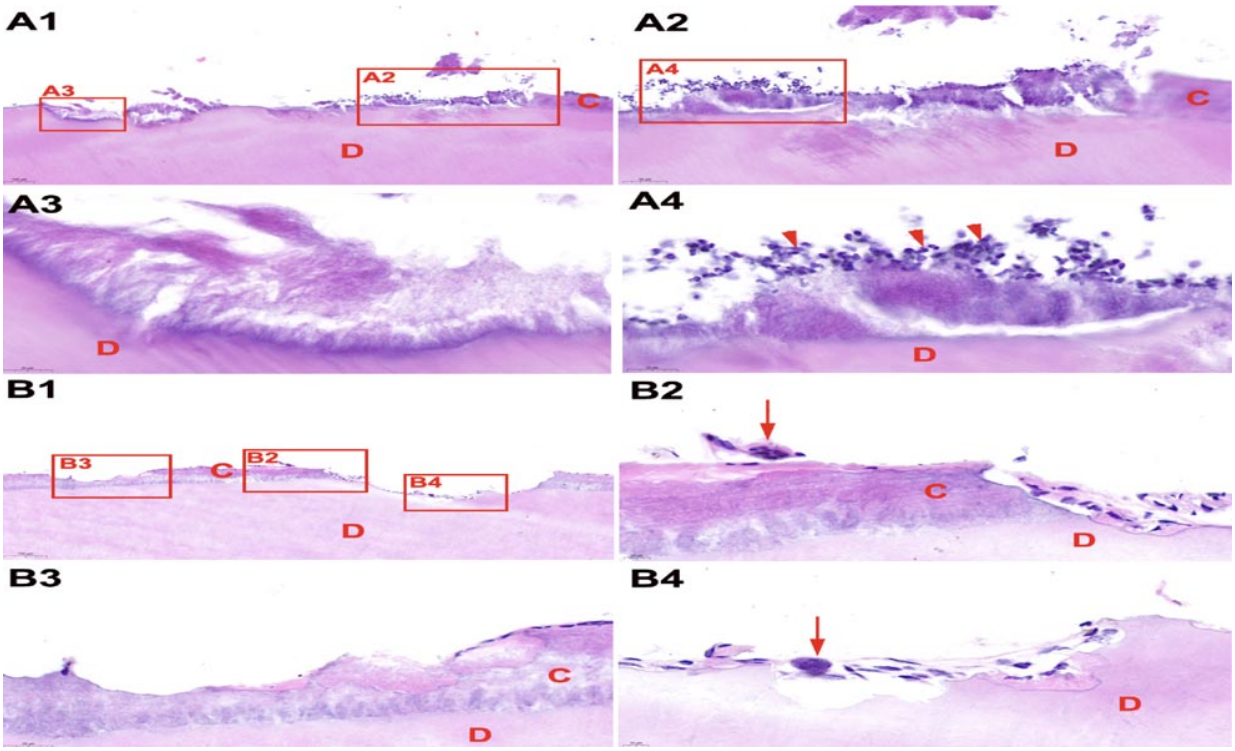

Fig. 2. Histological observation of the external root surface resorption in human severe periodontitis. External inflammatory resorption (A1 and B1) had occurred in human severe periodontitis, The loss of cementum (A2, A4, B2 and B3), even the loss of dentin (A3 and B4), inflammatory cells (red arrowheads) and multiple clastic cells (red arrows) were found in external inflammatory resorption sites.

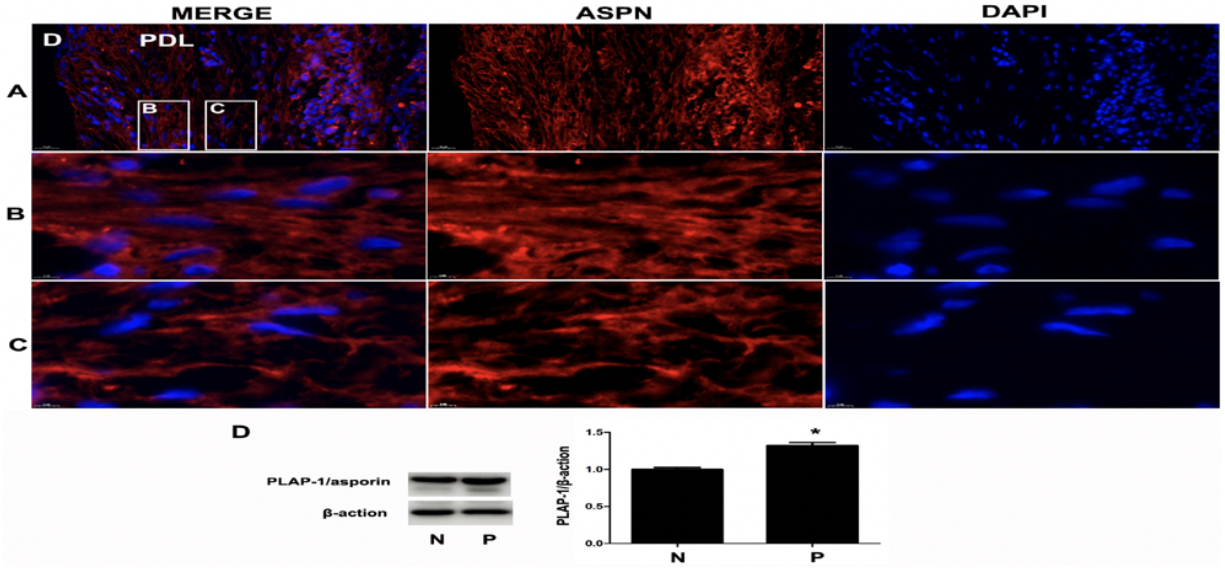

Fig. 3. Expression of Asporin/PLAP-1 in human periodontitis detected using immunofluorescence. The expression of PLAP-1/ asporin in the inflammatory tissues was also significantly higher than that in the normal periodontal ligament tissues, suggesting that PLAP-1/ asporin participates in periodontal inflammation.

Additionally, external inflammatory resorption was observed in the teeth with severe human periodontitis, and multiple clastic cells were identified around the resorption sites. Double-labeled immunofluorescence results further confirmed the co-localization of PLAP-1/asporin and CD68 in these multiple clastic cells, suggesting that PLAP-1/ asporin may participate in the process of external inflammatory resorption by acting on clastic cells (Fig. 5).

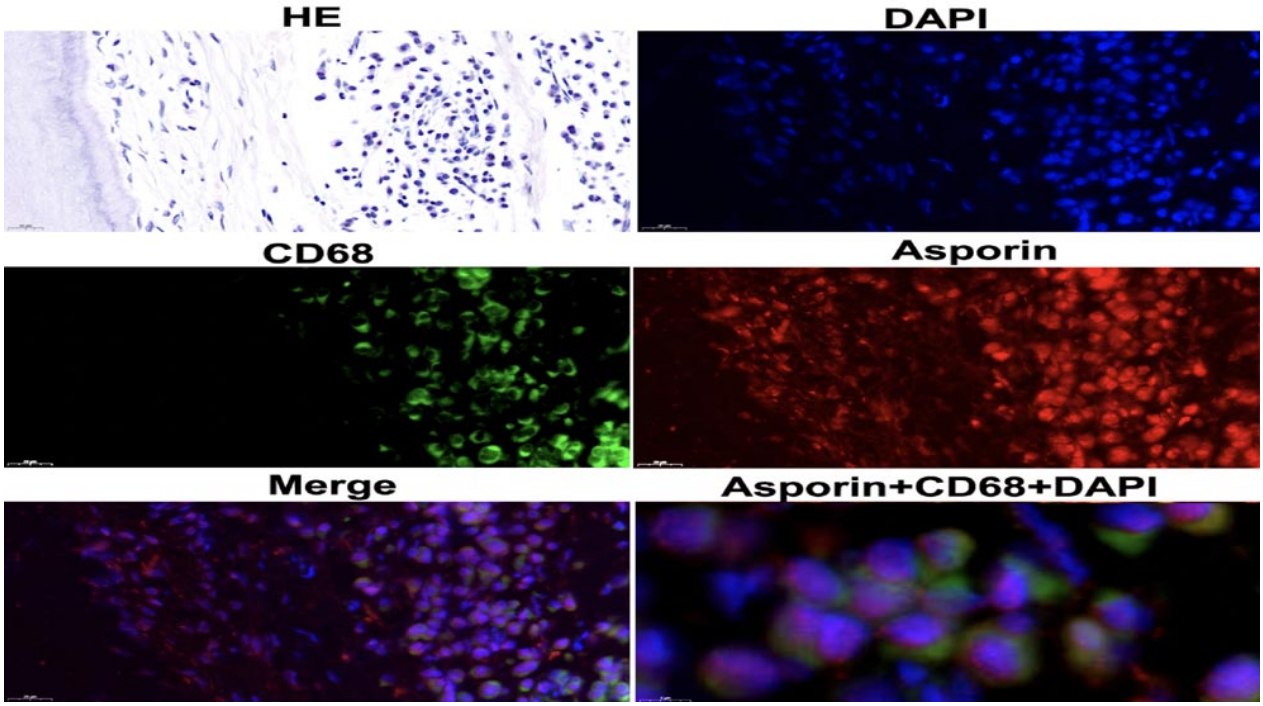

Fig. 4. Expression of Asporin/PLAP-1 in infiltrating inflammatory cells in human severe periodontitis. Many inflammatory infiltrating cells were observed in the periodontal ligament of severe human chronic periodontitis by HE. Immunofluorescence co-localization results showed Asporin/PLAP-1 positive expressions were also found in CD68-positive infiltrating inflammatory cells.

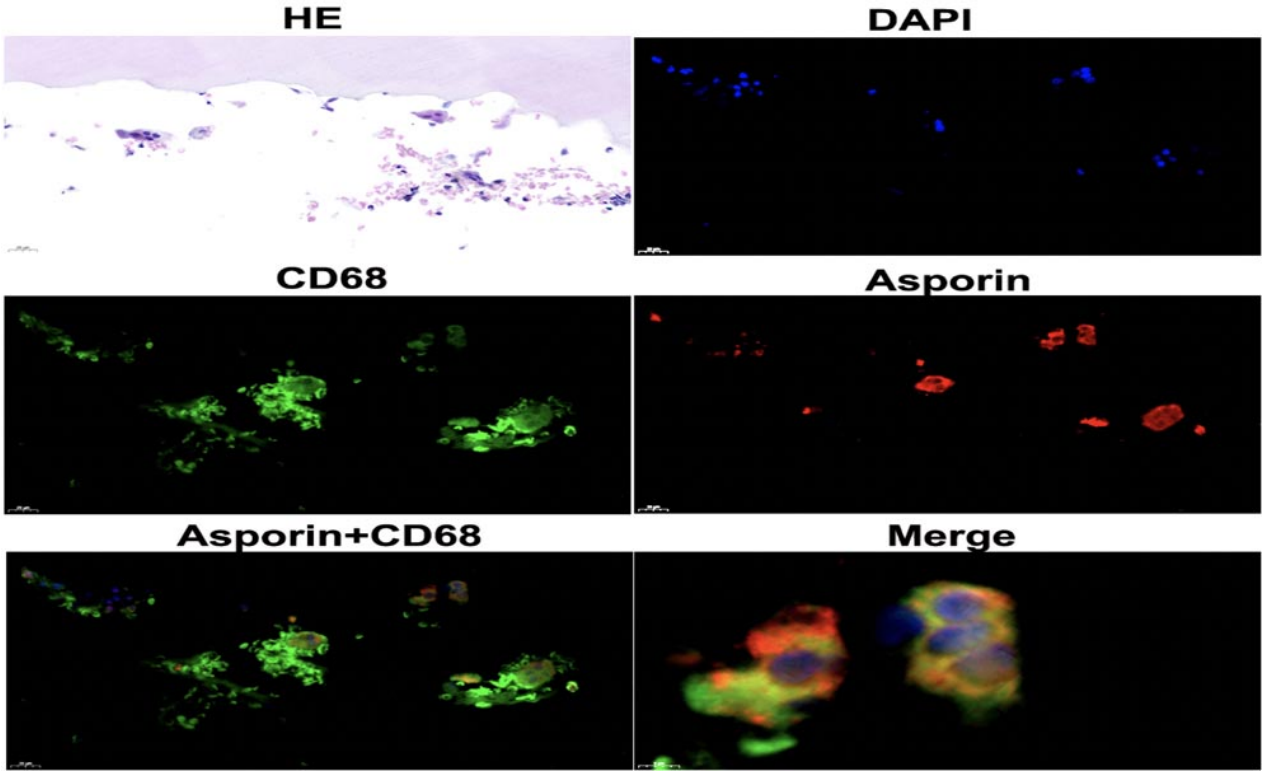

Fig. 5. Colocalization of Asporin/PLAP-1 and CD68 in multiple clastic cells. External inflammatory resorption could also be observed in human severe periodontitis. Multiple clastic cells were found around the external inflammatory resorption sites. Double-labelled immunofluorescence result revealed that Asporin/PLAP-1 and CD 68 were overlapped (yellow) in the multiple clastic cells, which resorb mineralized tissues.

DISCUSSION

Periodontal bacteria and/or their endotoxins in patients with severe chronic periodontitis have the potential to induce pathological changes in the dental pulp via lateral or accessory canals (Yu *et al*., 2020; Fang *et al*., 2021). If damage to the external root surface leads to the exposure of dentinal tubules, bacteria in the periodontal ligament (PDL) and/or their endotoxins can also readily migrate through these dentinal tubules to reach the root canal system (Rotstein & Simon, 2004). In the present study, histological analysis revealed varying degrees of inflammatory infiltration, tissue degeneration, and necrosis in the PDL of teeth with severe human periodontitis. These observations indicate that periodontal inflammation disrupts the stability of the PDL microenvironment. Although large areas of the root surface remained intact, external inflammatory resorption (characterized by the loss of cementum and, in some cases, dentin) was detected in teeth with severe periodontitis. Collectively, these findings suggest that periodontal pathogenic endotoxins may readily penetrate the exposed dentinal tubules to reach the root canal system, thereby contributing to the development of combined periodontal-endodontic lesions.

It is well established that PLAP-1/asporin is a key regulator in the maintenance of periodontal tissue homeostasis. Thus, the impact of the periodontal inflammatory microenvironment on PLAP-1/asporin expression warrants further investigation. PLAP-1/asporin exerts a defensive role in periodontitis lesions by regulating toll-like receptor 2 (TLR2)- and toll-like receptor 4 (TLR4)-induced inflammatory responses (Kamikawatoko *et al*., 2024). In the current study, our in vivo results showed that inflammatory stimulation increased the level of PLAP-1/asporin in the PDL of human periodontitis.

Previous studies have confirmed the involvement of asporin in common bone and joint diseases, including osteoarthritis (Ikegawa, 2008), rheumatoid arthritis, and lumbar disc disease (Ege *et al*., 2021). Asporin is primarily expressed in regions surrounding skeletal tissue and is upregulated in pathological states (Sasaki *et al*., 2021). Additionally, asporin levels are significantly increased in patients with temporomandibular joint disorders (Lall *et al*., 2024). Our earlier study reported an increase in PLAP-1-positive inflammatory infiltrating cells in a rat model of experimental periodontitis (Yu *et al*., 2019). In the present study, a large number of inflammatory infiltrating cells were observed in the PDL of human periodontitis, and PLAP-1/asporin expression was detected in CD68-positive infiltrating inflammatory cells. This finding further supports the notion that PLAP-1 is involved in the pathogenesis of human periodontitis. Furthermore, double-labeled immunofluorescence revealed co-localization of PLAP-1/asporin and CD68 in these clastic cells. These results indicate that both the PDL and root surface are affected by the inflammatory microenvironment in human periodontitis, and PLAP-1/asporin is involved in this pathological process.

Beyond periodontal and skeletal diseases, asporin is also predominantly expressed by cancer-associated fibroblasts (Lall *et al*., 2024). Intriguingly, conflicting roles of asporin in tumor progression have been reported: it is upregulated in breast, prostate, gastric, pancreatic, and colon cancers, but downregulated in triple-negative breast cancer (Lall *et al*., 2024; Ge *et al*., 2025). The complex behavior of asporin across different pathological contexts underscores the need to better understand its specific functions in the periodontal inflammatory microenvironment.

CONCLUSION

This study demonstrates PLAP-1/asporin upregulation in severe periodontitis and its co-localization with CD68-positive cells at resorption sites. Combined with elevated HIF-1a in affected pulps, these findings indicate their synergistic involvement in the inflammatory microenvironment of periodontal-endodontic lesions, providing new insights for mechanistic understanding and targeted therapy.

PAN, K.; LI, Z.; YI, X.; JIN, C.; ZHU, M.; YU, X. & XIAO, C. La PLAP-1/asporina participa en las alteraciones histológicas de la superficie radicular externa después de periodontitis grave en humanos. *Int. J. Morphol., 44(2)*:625-631, 2026.

RESUMEN: La PLAP-1/asporina es un regulador clave en el mantenimiento de la homeostasis periodontal. Sin embargo, su participación en las alteraciones histológicas de la superficie radicular externa tras periodontitis grave en humanos es poco documentada. En este estudio, se observó la superficie radicular externa en casos de periodontitis humana y se investigó el papel de la PLAP-1/asporina en este proceso patológico. Se observó infiltración inflamatoria, necrosis del tejido periodontal y reabsorción del cemento (e incluso de la dentina) en la superficie radicular externa de los dientes afectados por periodontitis grave. Además, se detectaron células inflamatorias y múltiples células clásticas alrededor de los sitios de reabsorción inflamatoria externa en casos de periodontitis humana grave. Cabe destacar que la expresión de PLAP-1/asporina en los tejidos inflamatorios fue significativamente mayor que en los ligamentos periodontales normales. También se identificó expresión positiva de PLAP-1/asporina en células inflamatorias infiltrantes CD68-positivas y múltiples células clásticas (responsables de la reabsorción de los tejidos mineralizados). En conjunto, este estudio correlaciona las alteraciones patológicas de la superficie radicular externa con la periodontitis grave y demuestra que PLAP-1/asporina participa en las alteraciones histológicas de la superficie radicular externa tras una periodontitis humana grave.

PALABRAS CLAVE: Proteína 1 asociada al ligamento periodontal; Asporina; Periodontitis; Reabsorción externa.

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