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Cyclophilin A (CypA) is associated with the inflammatory infiltration and alveolar bone destruction in an experimental periodontitis

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ABSTRACT

Background and objective: CypA is able to regulate inflammatory responses and MMPs production via interaction with its cell surface receptor, EMMPRIN. This study aimed to address the possible association of CypA with pathological inflammation and destruction of periodontal tissues, and whether CypA–EMMPRIN interaction exists in periodontitis. *Materials and methods:* Experimental periodontitis was induced by ligation according to our previous method. Histological and radiographic examinations were performed. Western blot was used to detect CypA and EMMPRIN expressions in gingival tissues. Immunohistochemistry was applied for CypA, EMMPRIN, MMP-1, MMP-2, MMP-9, as well as cell markers of macrophage, lymphocyte and neutrophil. CypA expression, alveolar bone loss, and inflammatory infiltrations were quantified followed by correlation analyses. *Results:* Western blot revealed that CypA and EMMRPIN expressions were dramatically elevated in inflamed gingival tissues (ligature group) as compared to healthy gingival tissues (control group). The enhanced CypA and EMMPRIN expressions were highly consistent in cell localization on seriate sections. They were permanently co-localized in infiltrating macrophages and lymphocytes, as well as osteoclasts and osteoblasts in interradicular bone, but rarely expressed by infiltrating neutrophils. MMP-1, MMP-2, and MMP-9 expressions were also sharply increased in inflamed gingiva. MMP-2 and MMP-9 were mainly over-expressed by macrophages, while MMP-1 was over-produced by fibroblasts and infiltrating cells. The number of CypA-positive cells was strongly correlated with the ACJ–AC distance ($r = 0.839$, $p = 0.000$), the number of macrophages ($r = 0.972$, $p = 0.000$), and the number of lymphocytes ($r = 0.951$, $p = 0.000$). *Conclusion:* CypA is associated with the inflammatory infiltration and alveolar bone destruction of periodontitis. CypA–EMMPRIN interaction may exist in these pathological processes.

Periodontitis is a kind of inflammatory disease characterized by the destruction of periodontal tissues. Matrix metalloproteinases (MMPs) play a crucial key role in the extracellular matrix degradation during periodontitis [1]. Extracellular matrix metalloproteinase inducer (EMMPRIN) is a plasma membrane protein best known for its ability to induce the production of MMPs [2]. We previously demonstrated that EMMPRIN was associated with the severity of inflammation and the production of MMPs in human periodontitis [3,4]. However, it is still not specifically known how EMMPRIN participates in the pathogenesis of periodontitis.

Other than induction of MMPs synthesis, EMMPRIN also functions as a cell surface receptor for cyclophilin A (CypA) [2,5]. CypA is originally known as the principal intracellular ligand for the potent immunosuppressive drug, cyclosporine (CsA). It also can be released extracellularly by cells in response to inflammatory stimuli [6]. CypA is able to regulate inflammatory responses via interaction with EMMPRIN [7]. CypA–EMMPRIN interaction also contributes to MMPs production from macrophages as well [8,9]. Although the pro-inflammatory and MMP-stimulating activities of CypA are well documented, there is no report on the possible involvement of CypA in periodontitis, and it is unclear whether CypA–EMMPRIN interaction contributes to the pathogenesis of periodontitis.

This study was designed, in an animal model, to address the possible association of CypA with the inflammation and destruction of periodontitis and whether CypA–EMMPRIN interaction exists in the pathogenesis of periodontitis.

Materials and methods

Animals. Forty-eight 6-week-old male Sprague–Dawley rats (200 ± 20 g body weight) were purchased from the Laboratory Animal Center of Wuhan University. They were housed under a 12-h

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light/dark cycle at 24 ± 2 °C with 40–60% humidity. The experiment was approved by Institutional Animal Care and Use Committee of Wuhan University.

Experimental periodontitis. Rats were randomly divided into two groups, control group and ligature group. Twenty-four rats from the ligature group were anesthetized with 20% urethane sodium chloride containing 20 g urethane and 100 ml normal saline (5 ml/kg body weight, intraperitoneal injection) and then subjected in accordance with our previous ligature method [10]. They were sacrificed the 7th day after ligation of the bilateral first mandible molars. The 24 control rats without ligation were killed as healthy controls on the same day. Gingival tissues (except papillae gingiva) around the bilateral mandible first molars were excised from each rat and immediately stored separately at −80 °C for Western blot. The remaining mandible tissues (with papillae gingiva) were used for radiographic and histological examinations.

Western blot. Total protein was isolated and the protein concentration was detected according to our previous methods [10,11]. PageRuler™ Prestained Protein Ladder (Fermentas AB) was used for molecular weight determinations. Protein samples (40 μg of protein per lane) were run in 10% SDS–PAGE (70 V for 2 h) and then transferred onto Hybond™ PVDF transfer membrane (Amersham Biosciences) using a humidified blotter. Membranes were washed with TBST buffer five times for 10 min (5 × 10 min) and blocked in 5% (w/v) skim milk for 2 h at 37 °C. Then membranes were incubated with antibodies against β-actin (1:1000, Pierce), CypA (1:1000, Abcam) and EMMPRIN (1:1000, Abcam) overnight at 4 °C. After being washed in TBST buffer again (5 × 10 min), membranes were incubated with a goat anti-rabbit HRP-conjugated IgG antibody (1:10,000, Pierce) for 2 h at 37 °C. Membranes were washed for another 5 × 10 min. ECL Western blotting system (Santa Cruz) was used for chemiluminescence according to the manufacturer's instructions. Blots were exposed to photographic films (KODAK). All antibodies were diluted in TBST buffer.

Radiographic and histological examinations. Each dissected mandible was attached to a plastic slab on the top of an X-ray film. To obtain a stable placement, the flat lingual side of mandible was placed downward. Radiographs were exposed for 12 s and developed automatically. Digital pictures were captured from X-gram by scanning. After radiographic examination, mandibles were sequentially fixed in 4% phosphate buffer formalin (pH 7.4) for 48 h, decalcified with 10% EDTA solution for 6 weeks at 4 °C, and processed for paraffin embedding. Mesiodistal sections were cut at 5 μm. After the sections were deparaffinized and rehydrated, they were stained with hematoxylin and eosin (HE) for histological examination. Alveolar bone loss was quantified by distance from amelocemental junction to alveolar crest (ACJ–AC) in interproximal area between the first and second molars. It was measured at the distal site of the first mandible molar by using computer software (SPOT RT v3.5), in accordance with our previous histometric distance method [10]. The measurements were performed on three sections for each rat. Quantitative analyses were carried out by a trained and calibrated examiner who was blind to the groups.

Immunohistochemistry. Sections were immersed in methanol with 0.3% hydrogen peroxide for 10 min to inactivate endogenous peroxidase. According to the pilot results, treatment to expose epitopes was unnecessary. Sections were rinsed with phosphate-buffered saline (3 × 5 min) before being covered with 10% normal serum for 20 min to block non-specific binding, and then incubated overnight at 4 °C with primary antibodies for EMMPRIN (1:300, Santa Cruz), CypA (1:400, Biomol), MMP-1 (2.5 μg/ml, Calbiochem), MMP-2 (1:150, Santa Cruz), MMP-9 (1:120, Santa Cruz), macrophage marker (1:50, Santa Cruz), lymphocyte marker (1:50, Santa Cruz), and neutrophil marker (1:50, Santa Cruz). After another rinse, sections were treated with secondary antibodies for 10 min and reacted with avidin–biotin–peroxidase complex for 10 min. Reaction products were visualized by immersing the sections in 0.03% diaminobenzidine solution for 5–10 min. Finally, sections were counter-stained with hematoxylin.

For each rat three sections were analyzed for CypA-positive cells. Each section was analyzed by counting the CypA-positive cells in nine randomly selected, separate 0.01 mm^2 areas in the supracrestal area between the first and second molars with a microscope (Olympus Optical Co. Ltd., Tokyo, Japan) under 40× magnification. The total numbers in nine areas were summed for each section, and averaged for each rat. The cells that positive stained for macrophage and lymphocyte markers were also counted to assess their infiltrations in a similar way.

Statistical analyses. All results were expressed as mean ± SD. Data were analyzed using SPSS statistical package. Kappa test was used for examiner calibration. Means were compared by using *T*-test. Linear regression was applied for correlation analyses. The null hypothesis was rejected at $p < 0.05$.

Results

Histological and radiographic examinations

Epithelial ulcer, vessel vasodilatation, disruption of collagen fibers, inflammatory infiltration, and alveolar bone loss were observed in the periodontal tissues of ligated rats (Fig. 1A). Collagen fibers were replaced by numerous infiltrating cells in gingival connective tissues. The infiltrating cells could be recognized as macrophages, lymphocytes, and neutrophils based on shape, size, and location. The height of alveolar crest in the interproximal area severely reduced and the amount of interradicular alveolar bone seriously decreased. Low density shadow was distinctly seen in both interproximal and interradicular areas on radiographs (Fig. 1B).

Over-expression and localization of CypA/EMMPRIN

Western blot revealed that the protein levels of both CypA and EMMRPIN considerably increased in the ligature group as compared to the control group (Fig. 1C). Immunohistochemistry demonstrated that the enhanced CypA and EMMPRIN expressions were mainly distributed in infiltrating cells (Fig. 2 A–D, a–d).

To examine the co-localization of CypA and EMMPRIN, their staining patterns were compared on seriate sections. Their localizations were highly consistent in the infiltrating area. The majority of the infiltrating macrophages and lymphocytes (>90%) were positive for CypA/EMMPRIN, in comparison to less than 10% of lobulated-nuclei neutrophils. CypA and EMMPRIN were co-localized in macrophages and lymphocytes, but rarely in neutrophils. They were also co-localized in some large multinucleate cells which were sporadically seen in connective tissues (Fig. 3A). In addition, CypA was distributed in the interradicular bone as well, with a great overlapping localization of EMMPRIN in large multinucleate osteoclasts in bone lacuna and square-shape active osteoblasts lining the surface of bone (Fig. 4A). Epithelial cells and odontoblasts were negative for CypA, but strongly positive for EMMPRIN under both healthy and pathological situations.

Localization of MMP-1, 2 and 9

It was demonstrated that CypA–EMMPRIN interaction contributed to MMP-2 and MMP-9 production by macrophages [7,8]. We previously determined an association of MMP-1 and MMP-2 with EMMPRIN in human periodontitis [4]. Therefore, to assess the association of these MMPs with CypA/EMMPRIN, we examined

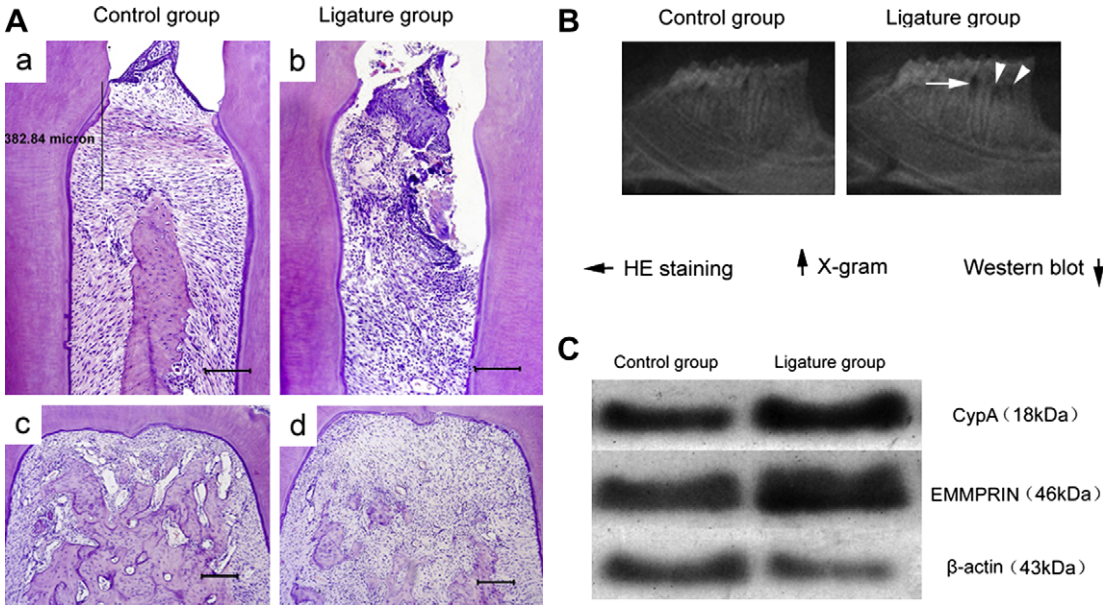

Fig. 1. (A) Histological examination by HE staining: intact structures in control group (a, c); vessel vasodilation, inflammatory infiltration and bone resorption in both interproximal area (b) and interradicular region (d) in the ligature group; the longitudinal line in panel (a) displays the ACJ–AC distance. Bar: 200 μm. (B) Radiographic examination on X-gram: arrow shows the interproximal bone loss; arrow heads show the interradicular bone resorption. (C) Over-expressions of CypA and EMMPRIN in inflamed gingival tissues detected by Western blotting. β-Actin was used as a loading control. Both CypA and EMMPRIN expressions considerably increased in the ligature group as compared to control group.

their expression and distribution by immunohistochemistry. This exposed a marked increase in the infiltrating area under the inflamed condition. The positive stained cells for MMPs were adjacent to those CypA/EMMPRIN-positive cells in the interproximal gingiva (Fig. 2 E–J, e–j). MMP-2 and MMP-9 showed increased localization in the infiltrating macrophages (Fig. 3B). A few spindle-sharp fibroblasts were also positively-stained for MMP-2. The enhanced MMP-1 production was distributed in both infiltrating cells and fibroblasts (Fig. 3B).

Inflammatory responses

One way that CypA contributes to inflammatory responses is its chemotactic activity via interaction with EMMPRIN. It can induce the migration of monocyte/macrophages [7,8], lymphocytes [12] and neutrophils [13] into tissues. Cell markers for these cells were immunostained to evaluate their infiltrations, although they could be recognized on HE-stained sections. Numerous positive cells were visible in gingival connective tissues under the inflamed condition (Fig. 3C). Most of the neutrophils were predominantly distributed near the gingival epithelium or within the gingival sulcus. Based on the localization of CypA/EMMPRIN in macrophages and lymphocytes, and limited localization in neutrophils, we decided to concentrate on the infiltrations for macrophages and lymphocytes. The quantitative analyzed results are shown in the following section.

Quantifications and correlation analyses

Alveolar bone loss, CypA expression, macrophage infiltration and lymphocyte infiltration were separately quantified by ACJ–AC distance, number of CypA-positive cells, number of macrophages, and number of lymphocytes. The Kappa test showed successful reproducibility for quantitative analyses (kappa > 0.75). The number of CypA-positive cells was 24.375 ± 5.547 in the ligature group, much higher than control group ($p < 0.01$). The ACJ–AC distance considerably increased from 414.083 ± 38.205 μm in the control group to 604.542 ± 95.093 μm in the ligature group ($p < 0.01$). The increased number of macrophages and lymphocytes was significantly in the ligature group in comparison to the amount observed in the healthy control ($p < 0.01$). These results were shown in Fig. 4B, a.

Correlation analyses revealed that the number of CypA-positive cells was strongly correlated with the ACJ–AC distance ($r = 0.839$, $p = 0.000$), the number of infiltrating macrophages ($r = 0.972$, $p = 0.000$), and the number of infiltrating lymphocytes ($r = 0.951$, $p = 0.000$) (Fig. 4B, b–d). Alternatively, CypA expression was highly correlated with alveolar bone loss, macrophage infiltration and lymphocyte infiltration.

Discussion

This in vivo study reports for the first time an over-expression of CypA in inflamed gingiva and its correlation with alveolar bone loss, macrophage infiltration and lymphocyte infiltration in periodontitis. These results indicate CypA may be associated with the inflammatory responses and alveolar bone destruction in periodontitis. We also determined highly-consistent localizations for CypA and EMMPRIN on seriate sections. They were co-localized in infiltrating macrophages and lymphocytes in inflamed gingival tissues, as well as in osteoclasts and osteoblasts in interradicular bone. Such overlapping localizations suggest that CypA–EMMPRIN interaction might exist in the pathogenesis of periodontitis.

CypA was primarily localized in infiltrating macrophages and lymphocytes in the inflamed gingival tissues. Similarly, Kim et al. have reported an over-expression of CypA by macrophages in rheumatoid arthritis synovium [8], but limited information is available on the expression of CypA by lymphocytes. Currently, the role of CypA in the function of lymphocytes with regard to inflammation is still unknown.

The localizations of EMMPRIN in macrophages and lymphocytes are consistent with previous findings that EMMPRIN is expressed by active T cells [14], macrophages [15], and monocytes [16]. It has been demonstrated that CypA–EMMPRIN interaction contrib-

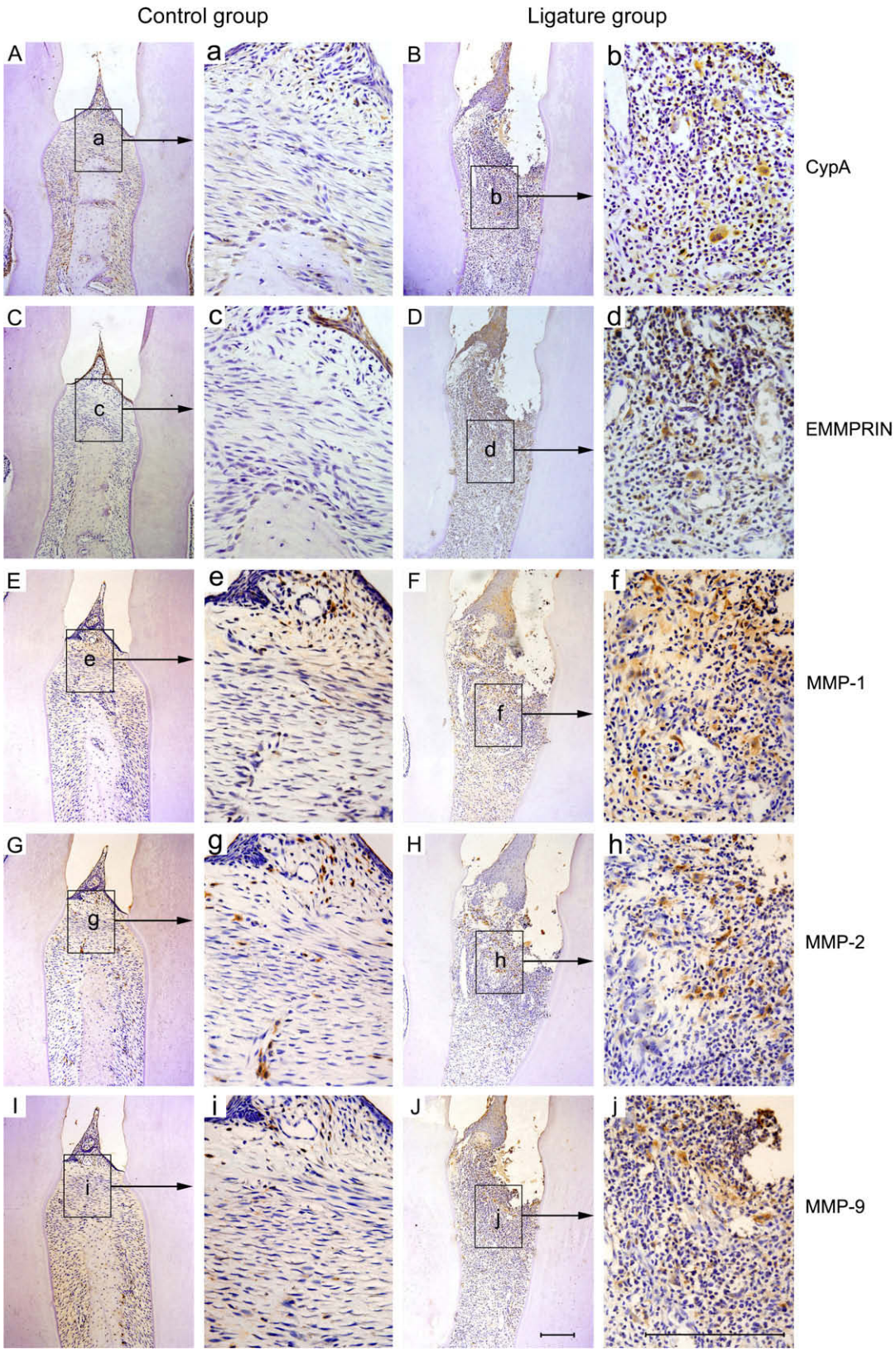

Fig. 2. Immunohistochemistry for CypA, EMMPRIN, MMP-1, MMP-2 and MMP-9 in interproximal gingiva on seriate sections. The positive staining was negative/weak in the healthy state (control group) for each of these molecules, and dramatically increased under the inflamed condition (ligature group). Bar: 200 μm.

utes to inflammatory responses via inducing the migration of monocyte/macrophages [7,8] and lymphocytes [12] into tissues. The EMMPRIN-positive inflammatory cells were deemed to be target cells for the CypA-induced inflammatory infiltrations because they could supply the binding-sites for CypA. Thus it was speculated that CypA might induce the infiltration of macrophages and

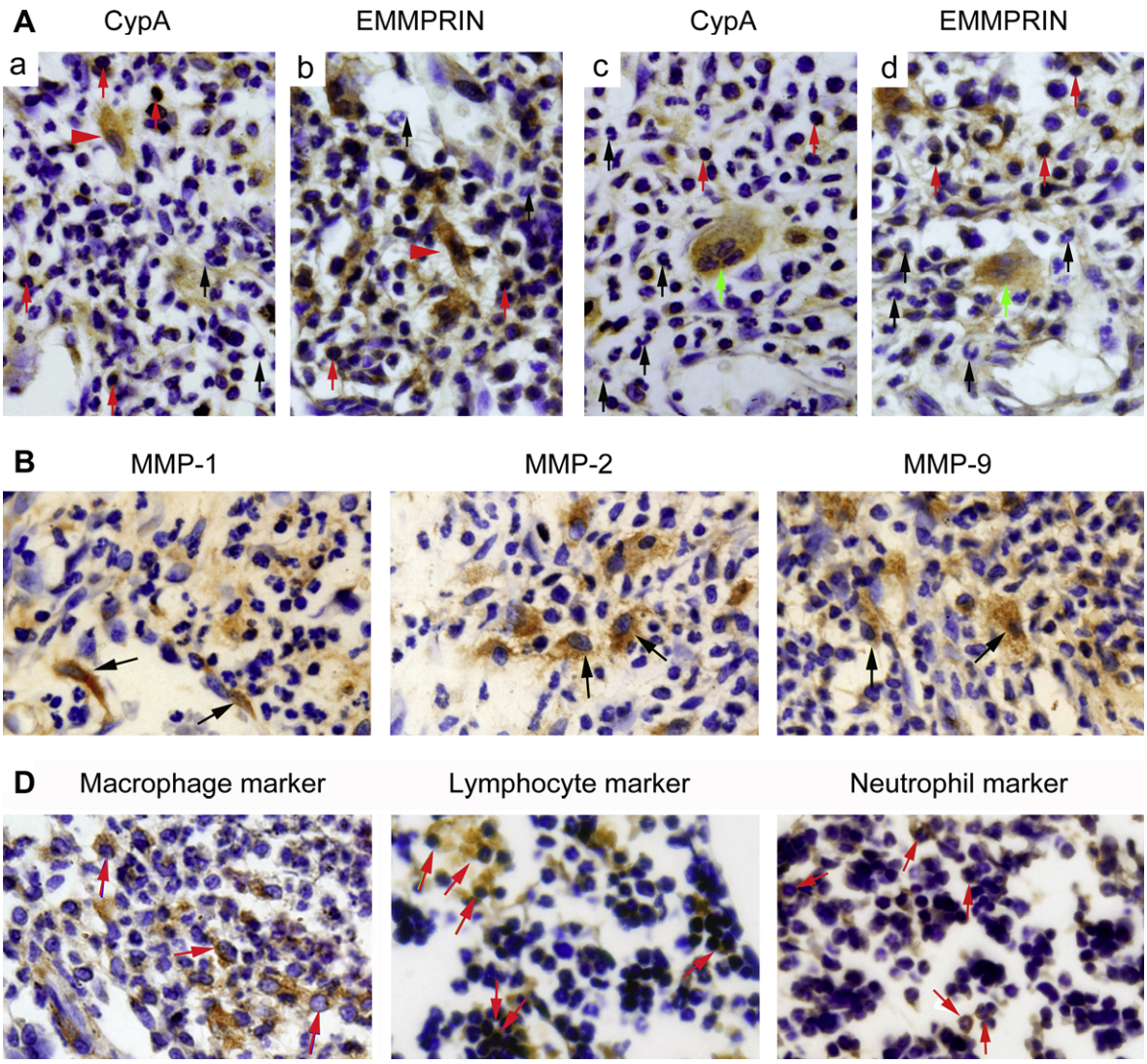

Fig. 3. Cell localizations of CypA, EMMPRIN, MMP-1, MMP-2, MMP-9 and cell markers in the inflamed gingival connective tissues: (A) CypA (a, c) and EMMRPIN (b, d) were co-localized in macrophages (red arrow heads) and lymphocytes (red arrows), as well as sporadically-seen large multinucleate cells (green arrow in (c) and (d)), but rarely in neutrophils (black arrows). (B) The over-expressed MMP-1 was localized in fibroblasts (black arrows) and infiltrating cells; while MMP-2 and MMP-9 were mainly localized in infiltrating macrophages (black arrows). (C) Macrophages, lymphocytes and neutrophils were stained brown by their cell markers (red arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

lymphocytes via interaction with EMMPRIN on their surface during periodontitis. This presumption was supported by the positive correlations of CypA expression with macrophage and lymphocyte infiltrations.

However, the positive staining for CypA/EMMPRIN was rarely seen in lobulated-nuclei neutrophils. It seems that the migration of neutrophils does not rely on CypA/EMMPRIN in this experimental periodontitis, although CypA–EMMPRIN interaction can regulate neutrophil chemotaxis [6,13]. This disagreement can be reasonably explained by the difference in immunological feature between human and rat. According to Klausen description [17], in contrast to man, which is a granulocytic species, rat is predominantly lymphocytic. Therefore, the granulocyte-related first line of defense against periodontal pathogens may be less efficient in rat than in man, and the lymphocyte-related immune response may be relatively more important. However, numerous neutrophils could be observed in the infiltrating area in this rat periodontitis model, although they were rarely positive for CypA/EMMPRIN. These inconsistencies are due to a lack of understanding and a subject that has yet to be further addressed.

Interestingly, CypA was also localized in osteoclasts and osteoblasts. Osteoclasts develop from a pluripotent mononuclear precursor [18]. It has been demonstrated that EMMPRIN can promote the maturation and activation of osteoclasts through facilitating the recruitment of circulating monocytes and macrophages [16,19]. Because of its ability to induce cell migration, CypA might contribute to osteoclastogenesis in a similar way. It would be beneficial to understand the association of CypA with alveolar bone loss, which was later confirmed by the correlation analysis for them. Actually, alveolar bone is constantly undergoing a remodeling process consisting of bone resorption followed by bone formation [20]. Thus, it is not difficult to understand the emergence of osteoblasts in the destructive periodontal condition. Unfortunately, no information is currently available on the expression of CypA by osteoblasts. Irrespectively, the localizations of CypA in both osteoblasts and osteoclasts indicate that it may be involved in the alveolar bone remodeling. Furthermore, such a CypA-related remodeling process might dependent on its interaction with EMMPRIN, in view of their greatly overlapped localizations in osteoblasts and osteoclasts.

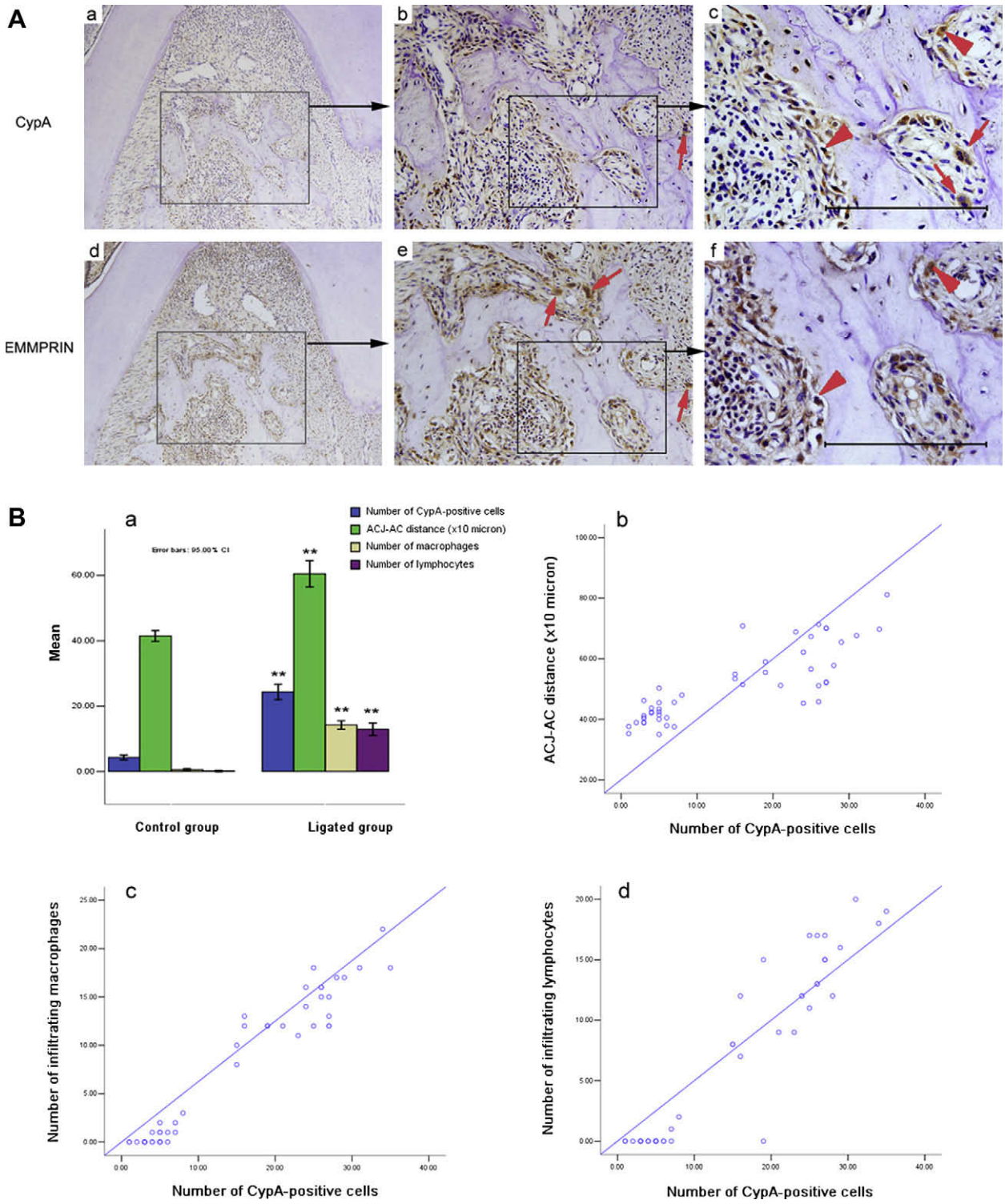

Fig. 4. (A) Co-localization of CypA (a–c) with EMMPRIN (d–f) in osteoclasts and osteoblasts in interradicular bone: the large multinucleate cells in bone lacuna were osteoclasts (red arrows); the square cells lining the bone surface were osteoblasts (red arrow heads). Bar: 200 μm. (B) Quantification and correlation analyses: (a) the ACJ–AC distance, the number of CypA-positive cells, macrophages and lymphocytes all significantly increased in the ligature group when compared with control group. $^{**}p < 0.01$; (b–d) the number of CypA-positive cells was strongly correlated with the ACJ–AC distance ($r = 0.839$, $p = 0.000$), the number of macrophages ($r = 0.972$, $p = 0.000$) and the number of lymphocytes ($r = 0.951$, $p = 0.000$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this paper.)

In addition, CypA was associated with endothelial cell activation and dysfunction [21,22]. In support of this notion, we found that CypA was also weakly expressed by endothelial cells, which was not described in detail. It is necessary to point out that CypA is not localized in gingival epithelial cells and odontoblasts, whereas EMMPRIN is strongly expressed by these cells under both healthy and inflamed conditions. The possible regulatory role of EMMPRIN in gingival epithelium metabolism that we previously described [4] is likely independent on CypA.

Immunohistochemistry has made it evident that MMP-1, MMP-2, and MMP-9 expressions were sharply increased in the interproximal gingiva of ligated rats. Kim et al. [8] found that CypA up-regulated MMP-9 expression and induced low level conversion of pro-MMP-2 into active form from monocyte/macrophages via EMMPRIN signaling pathway. The increased expressions of MMP-2 and MMP-9 in macrophages were consistent to these findings. Despite being fibroblast-type matrix metalloproteinase, MMP-2 was not frequently localized in fibroblasts. This finding was met with puzzlement. The raised MMP-1 expression was permanently localized in fibroblasts and infiltrating cells. Although it was related to EMMPRIN in human periodontitis [4], the direct connection of CypA with MMP-1 production is still not confirmed. This study does not provide formal proofs for the contribution of CypA/EMMPRIN interaction to these MMPs production, but further in-depth *in vitro* studies will elucidate these issues.

Several studies have probed into the possible role mechanisms for CypA and EMMPRIN. Human recombinant CypA activated mitogen-activated protein kinases, including ERK1/2, JNK, and p38 [21]. CypA-induced MMP-9 expression is dependent on NF-κB and MAPK activation [8,9]. EMMPRIN induced MMP-1 production in a mitogen-activated protein kinase (MAPK) manner [23], and MMP-2 expression through activation of A2 and 5-lipoxygenase [24]. However, the exact signaling pathway of CypA/EMMPRIN utilized during periodontitis is not completely understood and awaits more investigation.

Gwinn et al. [25] described an approach to inhibit asthma-mediated lung inflammation using anti-EMMPRIN to block the CypA–EMMPRIN interaction. Damsker et al. [26] also reported that anti-EMMPRIN could reduce the development of collagen-induced arthritis. A similar strategy would be worth consideration for treatment of periodontitis. It is of much interest and will be addressed in future works. From this aspect, this study, despite being a description one, not only sheds light on the pathogenesis of periodontitis, but also exposes new insight on the treatment of periodontitis.

To sum up, our findings indicate CypA is associated with the inflammatory responses and alveolar bone destruction in periodontitis, and CypA–EMMPRIN interaction might exist in these pathological processes. Based on the role of CypA–EMMPRIN interaction in the inflammatory responses and the production of MMPs, it is appropriate to conclude that CypA–EMMPRIN interaction may contribute to the pathological inflammation and destruction during periodontitis.

Acknowledgments

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