Comparative analysis of the immunohistochemical expression of collagen IV, MMP-9, and TIMP-2 in odontogenic cysts and tumors

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Objective. The aim of this study was to evaluate the immunohistochemical expression of collagen IV, matrix metalloproteinase (MMP) 9 and tissue inhibitor of MMP (TIMP) 2 in dentigerous cysts (DCs), radicular cysts (RCs), keratocystic odontogenic tumors (KOTs), and ameloblastomas.

Methodology. Twenty cases of DCs, 20 RCs, 20 KOTs, and 20 ameloblastomas were selected and analyzed by immunohistochemistry.

Results. Most DCs and RCs showed continuous and >50% staining for collagen IV in the basement membrane of the epithelium, whereas predominantly discontinuous thin and ≤50% staining was observed in KOTs and ameloblastomas, with a significant difference in staining percentage (P < .001). MMP-9 was diffusely distributed and localized in both epithelial and mesenchymal cells of all of the lesions analyzed. The staining percentage was higher in the epithelium (P = .058) and mesenchyme (P = .005) of KOTs and ameloblastomas. Moreover, the distribution pattern, location, and percentage of expression of TIMP-2 were similar in the lesions studied, except for ameloblastoma, with a significant difference in staining percentage (P < .001).

Conclusion. These results demonstrate that the interaction between collagen IV, MMP-9, and TIMP-2 is an important factor for the establishment of differences in the biologic behavior of the odontogenic cysts and tumors studied. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:468-475)

Factors related to the epithelial and mesenchymal components participate in the regulation of the growth of odontogenic cystic lesions and tumors. The altered expression of specific proteins of the extracellular matrix (ECM), associated with the exuberant presence of matrix metalloproteinases (MMPs) and the absence of expression of metalloproteinase inhibitors (TIMPs), may influence the behavior of these lesions. In the case of tumors, this situation contributes to the growth and higher aggressiveness of the tumor.

The odontogenic keratocyst, recently reclassified as keratocystic odontogenic tumor (KOT), is known for its aggressive nature and high rate of recurrence, especially compared with other odontogenic cysts. Ameloblastoma is a locally aggressive benign epithelial odontogenic tumor with a marked invasion potential that results in multiple recurrences after enucleation and curettage. In contrast, dentigerous (DC) and radicular (RC) cysts show an indolent behavior and rarely recur after surgical removal. KOT presents a cystic structure similar to that of DC and RC, but its invasive and destructive growth is similar to that of ameloblastoma.

KOT, ameloblastoma, DC, and RC show distinct evolutions and biologic behaviors. In view of this fact, a growing number of studies have tried to identify...
epithelial and mesenchymal factors that determine the differences in behavior between these diseases. These lesions arise from the remnants of odontogenesis, which is controlled by the interaction between epithelial and mesenchymal components.

Because odontogenic lesions sometimes mimic the events related to the morpho- and histodifferentiation necessary for tooth development, it is thought that during tumorigenesis, epithelial-mesenchymal interactions are also determinant for the evolution of these lesions. However, according to Oliveira et al.,7 many studies have investigated only the epithelial components of odontogenic cysts and tumors.

The growth mechanism of odontogenic cysts, as well as the invasion and destructive potential of some odontogenic tumors, might be influenced by the secretion of MMPs, proteins that can be produced by both epithelial and mesenchymal cells.8,9 Alaeddini et al.10 suggested that for a better understanding of the biologic behavior of these lesions, it is necessary to study the components of the extracellular matrix (ECM) to identify differences in the distribution and expression of these proteins between indolent cystic lesions and more aggressive tumors.

In view of the above considerations, the objective of the present study was to evaluate the immunohistochemical expression of collagen IV, MMP-9, and TIMP-2 in a series of cases of RC, DC, KOT, and ameloblastoma in order to contribute to a better understanding of the role of these proteins in the biologic behavior of these lesions.

MATERIAL AND METHODS

The sample consisted of 80 paraffin-embedded tissue specimens comprising 20 cases of solid ameloblastoma, 20 KOTs, 20 DCs, and 20 RCs, obtained from the Pathological Anatomy Service of the Discipline of Oral Pathology, Department of Dentistry, Federal University of Rio Grande do Norte (UFRN). The diagnoses of odontogenic cysts and tumors were made using the 1992 and 2005 World Health Organization classification criteria, respectively. The study was approved by the Research Ethics Committee of UFRN.

Immunohistochemical methods

For immunohistochemistry, 3 μm thick sections were mounted on glass slides previously prepared with organosilane adhesive (3-aminopropyltrithoxy-silane; Sigma Chemical Co.) and submitted to the streptavidin-biotin method. The histologic sections were deparaffinized in xylene and rehydrated in a decreasing alcohol series. The sections were submitted to antigen retrieval (Table I) and blockade of endogenous peroxidase with 10 volumes of hydrogen peroxide, washed in water, and incubated with Tris-HCl, pH 7.4, for 10 minutes. Next, the sections were incubated with the primary antibodies (Table I) diluted in 1% bovine serum albumin (BSA)/Tris-HCl, pH 7.4. The sections were then washed twice in phosphate-buffered saline solution (PBS) and treated with the labeled streptavidin biotin complex (LSAB; Dako, Carpinteria, CA) at room temperature to bind the primary antibodies. The reactions were developed with 0.03% diaminobenzidine (Liquid DAB+ Substrate; Dako) as chromogen, and the slides were counterstained with Mayer hematoxylin for 10 minutes. Finally, the sections were dehydrated in alcohol and cleared in xylene for mounting in Permount resin (Fisher Scientific) under a coverslip. Liver and bladder sections were used as positive control samples for MMP-9 and TIMP-2, respectively. Immunostaining of blood vessels in the basement membrane (BM) was used as internal positive control for collagen IV. Samples treated as described above, except that the primary antibody was replaced with a solution of BSA in PBS, served as negative control samples.

Immunostaining was evaluated by 2 examiners at different times under a light microscope. For collagen IV, immunoreactivity was analyzed at the BM at different times under a light microscope. The expression of MMP-9 and TIMP-2 was analyzed separately in the epithelial and mesenchymal components. In the mesenchymal component, staining was detected in fibroblasts and endothelial and inflammatory cells. Staining percentage was analyzed semiquantitatively according to the method of Fregnani et al.11: ≤50% stained cells and >50% stained cells. The distribution of staining was classified as focal and diffuse. The localization of staining in the epithelial component was classified as

Table I. Specifications of the antibodies used

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<th>Antibody</th>
<th>Manufacturer</th>
<th>Clone</th>
<th>Antigen retrieval</th>
<th>Dilution</th>
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follows: basal, suprabasal, and basal/suprabasal layer.

Immunohistochemical staining of collagen IV, MMP-9, and TIMP-2 was evaluated by descriptive and semiquantitative methods. Statistical analysis was performed using the SPSS for Windows program, version 7.0 (SPSS, Chicago, IL). The $\chi^2$ test was used to compare epithelial and mesenchymal staining. A $P$ value of < .05 was considered to indicate statistical significance.

**RESULTS**

Most DCs (65%) and RCs (55%) exhibited continuous staining for collagen IV in the BM of the epithelium (Fig. 1, a and b), whereas discontinuous staining predominated in KOTs (60%) and ameloblastomas (75%) (Fig. 1, c and d). Staining appeared thick or mixed in 70% of DCs and thin in 75% of RCs, 60% of KOTs, and 75% of ameloblastomas. The percentage of collagen IV expression differed significantly between lesions ($P < .001$). Immunostaining > 50% was observed in 70% of DCs and immunostaining ≤ 50% in 55% of RCs. The lowest staining percentage was observed for KOTs and ameloblastomas, with immunostaining ≤ 50% in 80% and 100% of the lesions, respectively (Table II).

Expression of MMP-9 was mainly diffuse in the epithelial and mesenchymal component of 100% of the lesions studied. There was minimal variation in the pattern of localization of stained cells. In the epithelium, staining was observed in all layers of 95% of DCs and 90% of RCs (Fig. 2, a and b), whereas in KOTs positive staining was detected throughout the epithelium in 100% of cases (Fig. 2, c). In ameloblastomas, staining was detected in both peripheral cells and in the center of islands of the neoplastic epithelium (Fig. 2, d). A staining percentage > 50% predominated in all lesions studied, with a trend to higher expression in KOTs (90%) and ameloblastomas (95%) compared with DCs (65%) and RCs (75%). However, there was no statistically significant difference ($P = .058$; Table II). Mesenchymal staining was observed in fibroblasts and inflammatory and endothelial cells in all cases studied. Regarding the expression of MMP-9 in the mesenchyme, staining percentage > 50% was higher in ameloblastomas (70%) and KOTs (40%), whereas only 25% of RCs and 20% of DCs exhibited > 50% stained cells ($P < .05$; Table II).
The expression of TIMP-2 was similar in all lesions, except for ameloblastoma. The distribution of staining was diffuse in the epithelium and connective tissue of 100% of DCs, RCs and KOTs (Fig. 3, a-c), whereas in ameloblastomas focal staining was observed in the epithelium of 55% of cases and diffuse staining in the connective tissue of 80% (Fig. 3, d). Positive staining of all epithelial cell layers was observed in 100% of DCs and RCs and in 95% of KOTs. In ameloblastomas, staining of peripheral epithelial cells and cells in the

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<th>Protein</th>
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<th>RC</th>
<th>DC</th>
<th>KOT</th>
<th>Ameloblastoma</th>
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Fig. 2. Immunohistochemical expression of MMP-9 (×400). Note the diffuse staining in the epithelium and mesenchyme in (a) dentigerous cyst (DC), (b) radicular cyst (RC), (c) keratocystic odontogenic tumor (KOT), and (d) ameloblastoma.
center of tumor islands was observed in 95% of cases. Mesenchymal staining was observed in fibroblasts and inflammatory and endothelial cells in all cases studied. The percentage of TIMP-2 staining in the epithelium was >50% in most lesions (100% DCs, 95% RCs, and 100% KOTs), whereas >50% stained cells were observed in only 55% of ameloblastomas \((P < .001; \text{Table II})\). In the mesenchyme, >50% stained cells were observed in 95% of DCs and in 100% of RCs and KOTs, whereas 55% of cases of ameloblastoma presented ≤50% stained cells \((P < .001; \text{Table II})\).

**DISCUSSION**

KOT, ameloblastoma, DC, and RC present distinct evolutions and biological behaviors. Despite the cystic structure of KOT, some studies emphasize the similarity in the behavior of these cysts to the ameloblastoma in view of their invasive growth and destructive potential.6

Several factors have been associated with the aggressive behavior of ameloblastomas, such as an increased proliferation potential,12 alterations in the expression of tumor suppressor genes, and the aberrant expression of cell cycle–regulating proteins,13 adhesion molecules,14 and MMPs and their inhibitors (TIMPs).15 In addition, Silveira et al.8 suggested that the mechanism of expansion of KOTs, DCs, and RCs may also be influenced, or even be conducted, by the secretion of MMPs. Thus, an exuberant expression of MMPs might be related to a higher aggressiveness of cystic lesions.

MMP-9 is known to play an important role in BM degradation owing to its ability to degrade collagen IV, the main BM component. However, a balanced action of activators and inhibitors of MMPs is necessary so that these proteins can exert their function. In this respect, TIMPs inhibit the active forms of MMPs.16 On the basis of these observations it could be suggested that the degradation of ECM is not dependent on the expression of a single MMP, but rather that the combined action of several MMPs and TIMPs is essential for the efficient degradation of the BM and interstitial stroma. Kumamoto et al.15 performed an immunohistochemical study and found that increased expression of TIMP-1 and TIMP-2 was related to weak immunoreactivity for MMP-9. According to those authors, it is possible that the TIMPs contribute to suppress tumor progression in ameloblastomas through the inhibition of MMP-9 activity.

Within this context, the evaluation of the expression of collagen IV, MMP-9, and TIMP-2 may contribute to
the understanding of the distinct biologic behavior of these odontogenic lesions. ECM proteins have been detected in several odontogenic cysts and tumors, but no investigation has explored the relationship between collagen IV, MMPs, and TIMPs in odontogenic cysts and tumors.

In the present study, a lower expression of collagen IV was observed in KOT and ameloblastoma. A possible explanation is that a higher degradation or a reduced synthesis of this protein occurred in these lesions. We speculate that both increased degradation and reduced synthesis of collagen may influence the aggressiveness of the lesions. A higher capacity to degrade the BM and other ECM components has been associated that with a higher destructive potential of the lesions. According to Nagatsuka et al., the expression of collagen IV may be correlated with the growth and aggressiveness of odontogenic cysts and tumors.

In normal and benign tissue, collagen IV has been reported to appear in a continuous, thick and strongly stained linear pattern. In the present study, RCs, and DCs generally exhibited a linear and continuous expression of collagen IV, in agreement with the staining pattern described for normal tissues. On the other hand, KOTs and ameloblastomas presented a highly discontinuous thin linear staining pattern, with ≥50% extension of the BM in 80% and 100% of cases, respectively. This finding might be related to the proliferative potential of these odontogenic tumors. The loss of BM integrity is known to favor alterations in epithelial-mesenchymal interactions that contribute to the mechanisms of cell differentiation and tumor proliferation.

Regarding the thickness of collagen IV staining, RCs presented an irregularity compared with the staining seen in DCs. Most RCs (75%) exhibited a thin line, whereas staining in DCs was characterized by thick and thin areas in 70% of specimens. It is therefore thought that in DCs the inflammatory infiltrate, which is a determinant component of the lesion, contributed to the lower expression of collagen IV, because those cells showed high staining percentage for MMP-9. On the other hand, the presence of an inflammatory infiltrate is a common finding in DCs, and MMP-9 secretion was possibly lower, a fact explaining the regular and thick collagen IV staining.

The percentage of collagen IV staining was more pronounced in DCs than in RCs, KOTs and ameloblastomas. However, 45% of RC cases showed a staining percentage similar to that of DCs. Therefore, the present results suggest that the weak expression of collagen IV, mainly observed in KOTs and ameloblastomas, may induce changes in the interaction between the epithelium and mesenchyme, contributing to the more aggressive growth of these lesions.

In agreement with the findings of the present study, Oliveira et al. observed differences in the composition of the BM of RCs, DCs, and KOTs. Those authors observed continuous and intense expression of collagen IV in RCs. On the other hand, KOTs exhibited thin, linear, markedly discontinuous and weak staining. According to those authors, the epithelial component of KOTs has a higher proliferative capacity than that of DCs and RCs, a fact supporting the distinct biologic behavior of those lesions. In addition, it is possible that this BM irregularity shown by KOTs favors the constant shedding of epithelial cells from the capsule and may be related to the higher recurrence rates of these tumors. Although consensus exists regarding the relationship between BM integrity and aggressiveness of the lesion, Poonsawat et al. found no association between the expression of BM components (laminin 1 and 5, collagen IV, and fibronectin) in RCs, DCs, and KOTs and the biologic behavior of these lesions. Therefore, in view of the functions of the BM, especially its involvement in the control of cell proliferation, differentiation, and invasion, it is evident how much these processes are altered in KOTs and ameloblastomas, a fact that can explain the more aggressive behavior of these tumors compared with RCs and DCs.

Considerable research effort has been devoted to the MMP subfamily of gelatinases/type IV collagenases, including MMP-2, referred to as gelatinase-A, and MMP-9, referred to as gelatinase-B, because of their ability to degrade type IV collagen and gelatins. Expression of gelatinases/type IV collagenases has been investigated in numerous tumors and has been shown to be associated with an invasive phenotype and metastatic potential of tumor cells. Preclinical trials have shown that squamous cell carcinomas express high levels of MMPs in vivo and that the inhibition of these enzymes in vitro and in animal models reduces the invasion potential and metastatic capacity of the tumor.

Regarding the expression of MMP-9 in odontogenic cysts and tumors, in the present study epithelial and mesenchymal cells of the lesions studied diffusely secreted this protein. This finding suggests a role of MMP-9 in tumor growth, because the protein is known to act on the remodeling of ECM and the degradation of bone matrix. However, the staining percentage of MMP-9 in the epithelial and mesenchymal component was markedly higher in KOTs and ameloblastomas than in RCs and DCs, with a staining percentage >50% being observed in 90% and 95% of cases, respectively. These findings suggest that the growth of these lesions is influenced by the secretion of MMPs. Therefore, the
more exuberant expression of MMP-9 in the odontogenic tumors analyzed suggest a possible participation of this protein in cell proliferation and differentiation and may explain the greater bone resorption, higher invasion potential, and poorer prognosis compared with DC and RC. The immunoreactivity to MMP-9 seen in both the epithelium and the mesenchyme of these lesions can be explained by the fact that the protein is produced by epithelial cells, fibroblasts, macrophages, plasma cells, lymphocytes, and neutrophils.

According to Vicente et al., MMP-2 and MMP-9 are involved in angiogenesis and tumor growth, a fact suggesting an association of these gelatinases with the aggressive behavior and unpredictable clinical course of some human neoplasms. Similarly to the present study, Silveira et al. observed more pronounced expression of some human neoplasms. Similarly to the present study, Silveira et al. observed more pronounced expression of MMP-9 in the mesenchymal component of KOTs compared with RCs and DCs, a finding supporting the hypothesis of a more aggressive behavior of this tumor compared with other cysts. In the study by Kumamoto et al., immunoreactivity to MMP-9 was stronger in the stroma of ameloblastomas than in the mesenchymal component of tooth germs, suggesting that an increased production of this protein by neoplastic cells is related to the transformation of odontogenic tissues and aggressiveness of this tumor. Ribeiro et al. also found intense immunostaining for this gelatinase in the parenchyma and stroma of ameloblastomas, indicating its possible participation in the growth of these tumors.

Curiously, combined analysis of the present results showed that KOTs and ameloblastomas, which presented higher expression of MMP-9 in epithelial and mesenchymal components, also exhibited low expression of collagen IV, which may result from higher BM degradation or reduced synthesis of collagen IV. We think that these findings suggest higher BM degradation in consequence of high expression of MMP-9. Some reports in the literature show that MMP-9 plays an important role in the degradation of the BM as a result of its ability to degrade collagen IV.

Nagase et al. and Verma and Hansch demonstrated that MMPs are weakly expressed by tissues under physiologic conditions, whereas high expression of these proteins is observed in neoplastic tissues, owing to an imbalance in the activity of MMPs and their inhibitors (TIMPs). In the present study, high percentage and diffuse expression of TIMP-2 was observed in epithelial and mesenchymal cells of DCs, RCs, and KOTs. In contrast, focal staining was detected in ameloblastomas, a finding possibly implying lower secretion of this protein which inhibits the activity of MMP-9. Similarly, the staining percentage was less pronounced in the epithelial and stromal components of ameloblastoma compared with the other lesions, a finding suggesting higher production of MMP-9, increased BM degradation and the consequent higher invasion potential of this tumor. Siqueira et al. observed intense and diffuse TIMP-2 staining in ameloblastomas, which was associated with lower aggressiveness of the tumor. In an in vitro study, Wang et al. showed that overexpression of TIMP-2 in ameloblastoma cells was associated with the suppression of MMP-2 activity and a consequently lower invasion potential. It is believed that TIMP-2 suppresses tumor invasion by inhibiting MMPs. Taken together, these studies suggest that in the present series, the lower expression of TIMP-2 in ameloblastomas might be an indicator of the more aggressive behavior of this tumor compared with the other lesions studied, a fact supported by the higher expression of MMP-9.

The higher expression of TIMP-2 in DCs and RCs seems to be the result of a lower activity of MMP-9 and lower BM degradation, which is compatible with the more indolent behavior of these lesions. The balance between MMPs and TIMPs ultimately determines the extent of ECM degradation under physiologic and pathologic conditions. These features suggest that TIMP-2 may suppress tumor progression in ameloblastomas.

Immunoreactivity to MMP-9 and TIMP-2 was observed in the epithelial and mesenchymal components of all odontogenic lesions studied herein. This finding suggests that, similar to odontogenesis, epithelial-mesenchymal interactions are determinant for the regulation of the growth of cystic lesions and for tumor progression.

In conclusion, the present results suggest an interaction between the production of MMP-9 and TIMP-2 and the degradation of BM components, which may contribute to the distinct biologic behavior of ameloblastomas and KOTs compared with DCs and RCs. Ameloblastomas and KOTs demonstrate higher production of MMP-9 and increased degradation or reduced synthesis of collagen IV. The expression of these molecules may serve as an indicator of the degree of local aggressiveness of these odontogenic cysts and tumors.

REFERENCES


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