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Expression of extracellular matrix proteins in ameloblastomas and adenomatoid odontogenic tumors

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Abstract This study evaluated the expression of fibronectin, tenascin and type I collagen in ameloblastomas and adenomatoid odontogenic tumors (AOTs) aiming to contribute with the comprehension of the differences in the biological behavior of these tumors. Immunohistochemical technique was performed in 20 cases of ameloblastoma (16 solid and 4 desmoplastic) and in 10 cases of AOT. All tumors presented moderate fibronectin expression in the stroma. Solid ameloblastomas showed intense expression of fibronectin at the epithelial–mesenchymal interface, whereas desmoplastic ameloblastomas revealed no immunoexpression of fibronectin at this site. Ameloblastomas presented stronger immunoreactivity to tenascin than AOTs, especially at the epithelial–mesenchymal interface. AOTs and desmoplastic ameloblastomas showed intense labeling for type I collagen. The patterns of expression of the proteins studied agree with the locally more invasive behavior of ameloblastomas in comparison to AOTs. Our results might suggest a less invasive behavior of desmoplastic ameloblastoma in comparison to solid ameloblastoma.

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Introduction

Ameloblastoma is a benign epithelial odontogenic tumor, with mature fibrous stroma without odontogenic ectomesenchyme, which has been extensively studied due to its locally infiltrative behavior [1]. Adenomatoid odontogenic tumor (AOT), although being composed by odontogenic epithelium embedded in a mature connective tissue stroma, commonly shows an indolent evolution [2, 3].

Recently, ameloblastomas have been classified in four distinct subtypes: solid, unicystic, peripheral, and desmoplastic [1]. In solid ameloblastomas, the neoplastic cells can be arranged in different histopathological patterns, such as: follicular, plexiform, acanthomatous, granular cell, and basal cell [1]. This histological diversity can be observed between different cases but more than one morphological pattern can also be present within the same lesion [4]. In desmoplastic ameloblastomas, the stromal component dominates, compressing the islands of odontogenic epithelium, which are irregular in shape with a pointed, stellate appearance [1]. Ameloblastomas presenting both desmoplastic and other conventional histological patterns have been termed as hybrid lesions [1, 5]. In contrast, AOT show peculiar and frequently constant, histological characteristics [2].

In view of their intriguing biological behavior, ameloblastomas have been the subject of numerous studies that employed different methodologies. Most investigations have focused on the characteristics of the epithelial component that constitutes the tumor parenchyma [6–9] while few studies have analyzed the properties of the extracellular matrix (ECM), which constitutes the tumor stroma [10–13].

The ECM provides support and nutrients to cells, promotes cell adhesion and migration, and serves as a storage site for growth factors, thus influencing cell growth, morphology, and differentiation [14–16]. Based on these considerations, the objective of the present study was to analyze the expression of the ECM proteins fibronectin, tenascin and type I collagen in order to obtain data that, together with those obtained in studies on the differentiation and proliferation pattern of parenchymatous cells from ameloblastomas and AOT, might contribute to a better understanding of the biological behavior of these tumors.

Materials and methods

The present sample consisted of 20 cases of ameloblastoma (16 solid and 4 desmoplastic) and 10 AOT randomly selected from the files of the Anatomical Pathology Service, Discipline of Oral Pathology, Federal University of Rio Grande do Norte, Brazil. The paraffin-embedded specimens were collected and evaluated in accordance with all ethical and legal requirements.

Paraffin-embedded material was cut into 3-μm thick sections and stained by immunohistochemistry. Briefly, specimens were deparaffinized, hydrated in a decreasing ethanol sequence and formalin pigment was removed with 10% ammonium hydroxide in 95° ethanol. For tenascin and fibronectin, prior to incubation with primary antibodies, the samples were treated with 0.4 and 1% pepsin, respectively, at 37°C for 60 min. For type I collagen, specimens were treated with citric acid in a steamer for 5 min. Endogenous peroxidase was blocked by the addition of methanol–hydrogen peroxide solution. The specimens were then incubated with the following primary antibodies: anti-tenascin (clone TN2, Dako A/S, Glostrup, Denmark; diluted 1:50, overnight at 4°C), anti-fibronectin (clone A 0245, Dako A/S; diluted 1:600, for 120 min at room temperature), and anti-type I collagen (clone NCL-COLL-Ip, Novocastra Laboratories; diluted 1:40, for 60 min at room temperature). The material was immersed in Tris buffer, pH 7.4, between the reactions steps. The specimens were then incubated with the second antibody and the streptavidin–biotin complex (SABC, Dako) for 30 min at room temperature to bind the primary antibodies. Peroxidase activity was visualized by immersing tissue sections in diaminobenzidine (D5637; Sigma Chemical, St. Louis, MO, USA). Finally, tissue sections were counterstained with Mayer hematoxylin and coverslipped. Positive controls for tenascin and fibronectin were sections of normal oral mucosa. Positive control for type I collagen were sections of human placenta. An irrelevant, isotype-matched antibody was used as a negative control instead of primary antibodies.

After the immunohistochemical treatment, tissue sections were analyzed by light microscopy. The immunoreactivity was evaluated in terms of intensity and pattern of labeling. The distribution of these proteins was evaluated in tumor stroma, epithelial–mesenchymal interface and tumor cells. Comparisons were performed between ameloblastomas and AOT, as well as between different histopathological patterns of ameloblastoma.

Results

In all ameloblastomas, morphological analysis disclosed the existence of more than one histological pattern. Solid ameloblastomas represented 16 cases and revealed mainly follicular and plexiform areas. In four cases, areas of desmoplastic ameloblastoma were associated to other histological patterns, representing hybrid lesions. In all specimens of AOT, morphological analysis revealed variably sized nodules of cuboidal and columnar cells forming nests or rosette-like structures within a scarce stroma of connective tissue. Deposits of eosinophilic amorphous material were observed in the center of rosette-like structures. In addition, all cases presented a variable number of duct-like structures lined by a single role of columnar epithelial cells.

Fibronectin

All cases of solid and desmoplastic ameloblastoma exhibited fibronectin immunoexpression throughout the tumor stroma, which was mainly diffuse, fibrillar, and with moderate intensity (Table 1). At the epithelial–mesenchymal interface, solid ameloblastomas showed an intense, linear, and discontinuous expression of this protein (Fig. 1a). Desmoplastic ameloblastomas showed no expression of fibronectin at the epithelial–mesenchymal interface (Fig. 1b). Follicular areas of solid ameloblastomas revealed focal expression of fibronectin within epithelial tumor nests, both in areas resembling the stellate reticulum and in cells adjacent to foci of cystic degeneration (Fig. 1c).

In all cases of AOT, moderate to intense fibronectin expression was found scattered throughout the stroma (Table 1). Intense, linear and discontinuous labeling was observed at the epithelial–mesenchymal interface (Fig. 2a). Only few cases showed sparse foci of epithelial cell labeling.

Tenascin

Tenascin immunoexpression was characterized by a moderate to intense, diffuse and heterogeneous labeling in the stroma of all ameloblastomas (Table 2). Labeling was mainly observed adjacent to tumor nests, and was markedly intensified at the epithelial–mesenchymal interface

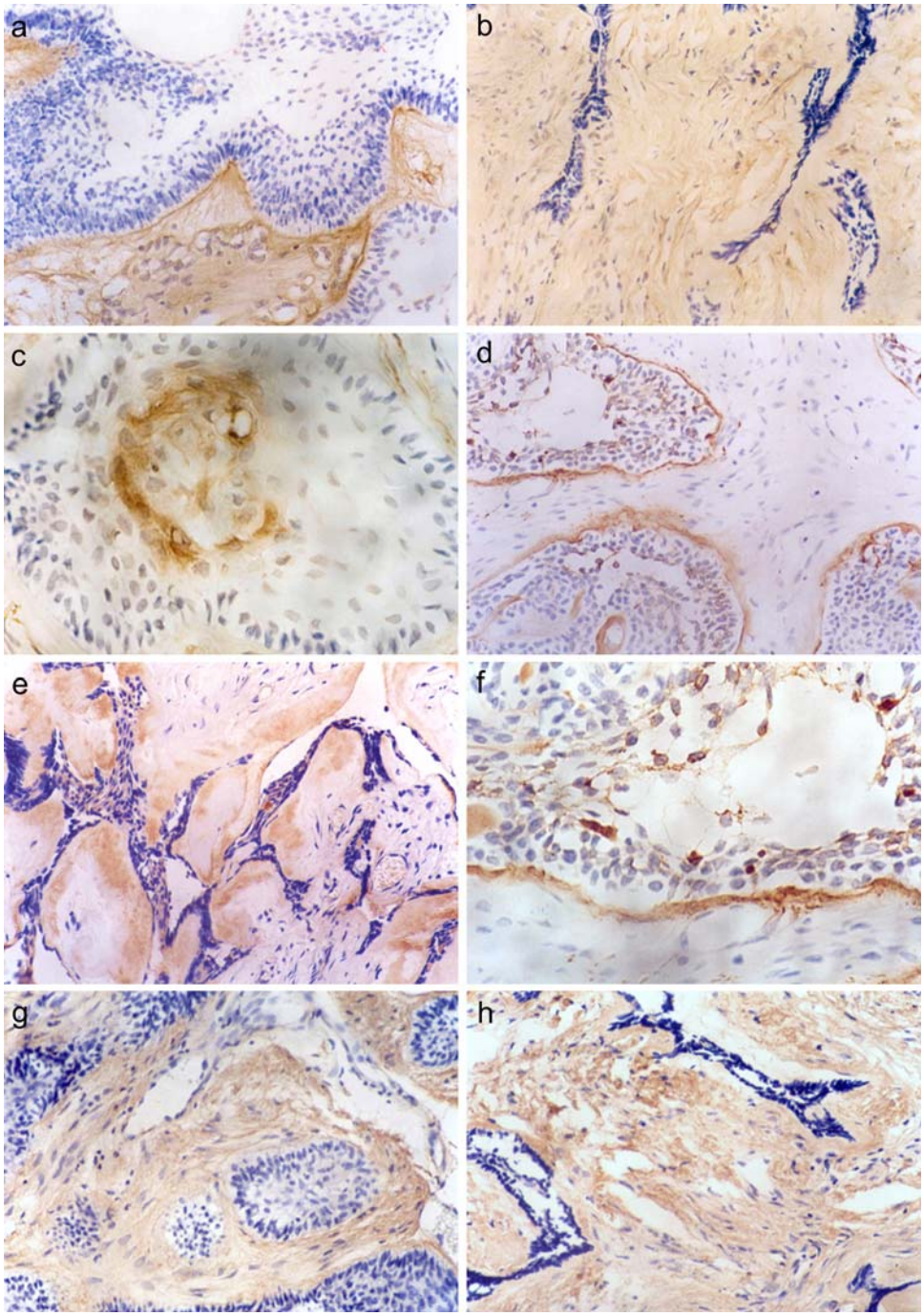

Fig. 1 Immunohistochemical staining of ameloblastomas. **a** Intense and discontinuous expression of fibronectin at the epithelial–mesenchymal interface and moderate immunoreaction in the tumor stroma of solid ameloblastoma (SABC 200×). **b** Moderate fibrillar positivity of fibronectin throughout the tumor stroma of desmoplastic ameloblastoma (SABC 200×). **c** Expression of fibronectin in epithelial tumor nest of solid ameloblastoma (SABC 400×). **d** Marked linear immunoexpression of tenascin at the epithelial–mesenchymal interface of solid ameloblastoma (SABC 200×). **e** Remarkable immunoreaction of tenascin at the epithelial–mesenchymal interface of desmoplastic ameloblastoma (SABC 200×). **f** Tenascin expression observed in epithelial islands and in the basement membrane zone of solid ameloblastoma (SABC 400×). **g** Fibrillar immunolabeling of type I collagen observed in the neoplastic stroma of solid ameloblastoma (SABC 200×). **h** Intense positivity of type I collagen in the tumor stroma of desmoplastic ameloblastoma (SABC 200×)

showing a linear, discontinuous pattern accompanied by enlarged foci (Fig. 1d, e). On the other hand, tenascin expression showed an amorphous and homogenous distribution in areas of stromal degeneration in plexiform areas of solid ameloblastomas. Follicular areas of solid ameloblastomas showed significant expression of tenascin within epithelial islands in areas resembling stellate reticulum and with cystic degeneration (Fig. 1f).

Analysis of the expression of tenascin in the stroma of AOT disclosed a variable intensity (Table 2; Fig. 2b). Focal areas of marked immunolabeling of this protein were observed close to the tumor parenchyma.

Type I collagen

Moderate to intense immunolabeling for type I collagen was observed in the stroma of all solid and desmoplastic ameloblastomas (Table 3). In comparison with solid ameloblastomas, desmoplastic ameloblastomas exhibited higher intensity of expression of type I collagen, always with a

Table 1 Pattern of distribution and intensity of the immunoreactivity for fibronectin in tumor stroma, epithelial–mesenchymal interface and epithelial cells

Specimen	Tumor stroma		Epithelial–mesenchymal interface		Epithelial cells
	Pattern	Intensity	Pattern	Intensity	
Solid ameloblastoma (n = 16)					
Follicular areas	Fibrillar	Moderate	Linear and discontinuous	Moderate to intense	Focal positivity
Plexiform areas	Fibrillar to fibro-reticular	Moderate	Linear and discontinuous	Intense	No staining
Basal cell areas	Fibrillar	Intense	Linear and discontinuous	Intense	No staining
Desmoplastic ameloblastoma (n = 4)	Fibrillar	Moderate	No staining	No staining	No staining
Adenomatoid odontogenic tumor (n = 10)	Fibrillar to fibro-reticular	Moderate to intense	Linear and discontinuous	Intense	Focal positivity

fibrillar pattern (Fig. 1g, h). Plexiform areas of solid ameloblastomas revealed an occasional immunoreactivity for type I collagen, particularly in foci of stromal degeneration.

AOT showed type I collagen immunoreactivity in all cases, mainly with an intense and fibrillar to fibro-reticular labeling throughout the tumor stroma (Table 3). Some specimens exhibited irregular accumulation of type I collagen between epithelial cells and inside some duct-like structures (Fig. 2c, d).

Discussion

In order to elucidate the mechanisms beneath the locally aggressive behavior of ameloblastomas, many studies have been performed, most of them aimed at the characterization of the cell cycle and pattern of differentiation of tumor parenchymatous cells [7–9]. Based on the assumption that both in physiologic and pathological conditions, cell growth and differentiation are influenced by cell–ECM interactions the study of the characteristics of ECM might be important to understand these relationships in tumor development. Previous studies have indicated a fundamental role for ECM in the development of neoplasms [13, 16–18].

Recent studies have shown that the ECM does not only act passively as a support for cells, but also provides information to these cells modifying their behavior, an event that might be responsible for tumorigenesis [16–20]. Among the ECM components, some proteins are important due to their regulatory or structural functions. Fibronectin is a glycoprotein, which possesses an important signaling function in cell adhesion and migration [5, 17, 20–23].

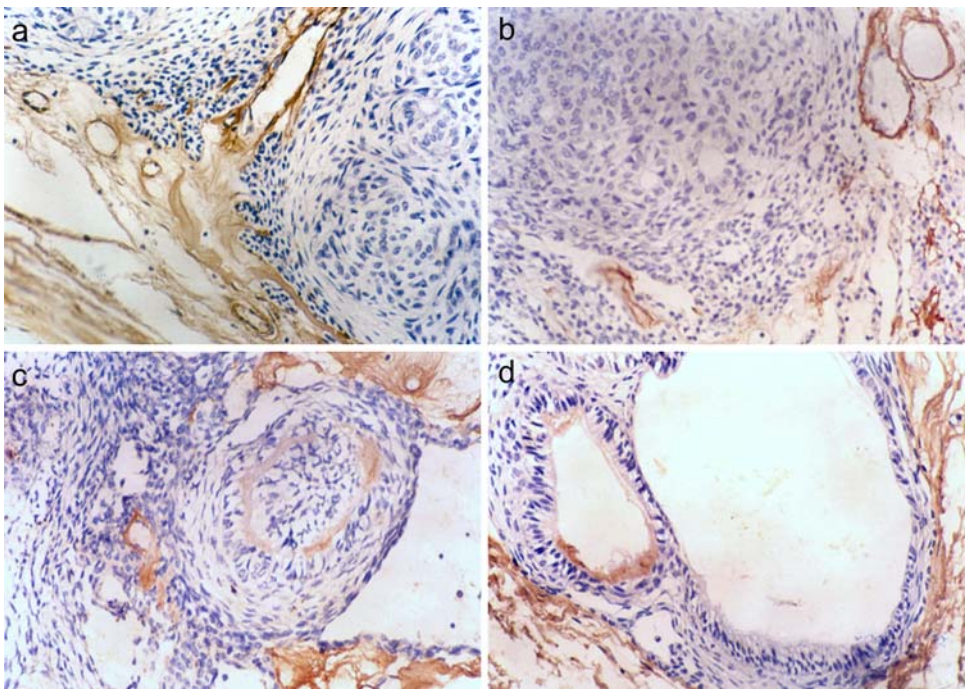

Fig. 2 Immunohistochemical staining of adenomatoid odontogenic tumors. **a** Immunolabeling of fibronectin throughout the tumor stroma and marked immunoexpression at the epithelial–mesenchymal interface (SABC 200×). **b** Focal areas of marked fibrillar immunolabeling of tenascin in the stroma and evident immunoreaction in blood vessels wall (SABC 200×). **c** Intense and diffuse labeling of type I collagen observed in the stroma and irregular accumulation between epithelial cells (SABC 200×). **d** Immunoexpression of type I collagen inside duct-like structure (SABC 200×)

Table 2 Pattern of distribution and intensity of the immunoreactivity for tenascin in tumor stroma, epithelial–mesenchymal interface and epithelial cells

Specimen	Tumor stroma		Epithelial–mesenchymal interface		Epithelial cells
	Pattern	Intensity	Pattern	Intensity	
Solid ameloblastoma (n = 16)					
Follicular areas	Fibrillar to fibro-reticular	Moderate	Linear and discontinuous	Moderate to intense	Positivity
Plexiform areas	Fibrillar to fibro-reticular	Weak to moderate	Linear and discontinuous	Weak to intense	No staining
Basal cell areas	Fibrillar	Moderate to intense	Linear and discontinuous	Moderate to intense	No staining
Desmoplastic ameloblastoma (n = 4)	Fibrillar	Intense	Linear and discontinuous	Moderate	Positivity
Adenomatoid odontogenic tumor (n = 10)	Fibrillar to fibro-reticular	Weak to moderate	Linear and discontinuous	Weak	Focal positivity

Table 3 Distribution of cases according to the pattern and intensity of the immunoreactivity for type I collagen in tumor stroma

Specimen	Tumor stroma		Epithelial cells
	Pattern	Intensity	
Solid ameloblastoma (n = 16)			
Follicular areas	Fibrillar to fibro-reticular	Moderate to intense	No staining
Plexiform areas	Fibrillar to fibro-reticular	Moderate to intense	No staining
Basal cell areas	Fibrillar	Moderate to intense	No staining
Desmoplastic ameloblastoma (n = 4)	Fibrillar	Intense	No staining
Adenomatoid odontogenic tumor (n = 10)	Fibrillar to fibro-reticular	Intense	Focal positivity

Tenascin is another glycoprotein synthesized at specific time points and sites during embryogenesis. The highest expression of tenascin is observed in unstable environments such as during cell migration, in active areas of epithelial–mesenchymal interactions, and in neoplastic stroma [14, 16, 18, 24]. Type I collagen is found throughout the connective tissue and is one of the most abundant components of the interstitial ECM [5, 23, 25], being highly resistant to proteases due to its unique supercoiled triple helix structure [26–28].

In the present study, the expression and distribution of fibronectin, tenascin, and type I collagen were analyzed in ameloblastomas and AOT. Few investigations about the ECM composition in odontogenic cysts and tumors have been carried out [10–13, 29, 30].

Our findings reveal a wide distribution of fibronectin in the stroma of solid ameloblastomas, desmoplastic ameloblastomas, and AOT. In AOT, a heterogeneous expression, with moderate intensity, was found scattered throughout the tumor stroma and in areas close to the parenchyma. Murata et al. [30] and Poomsawat et al. [13] suggested that AOT cells, like pre-ameloblasts, are able to synthesize ECM proteins due to the presence of fibronectin inside the luminal spaces of duct-like structures. Although this latter finding could not be verified in the present study, the focal positivity for fibronectin in epithelial cells of AOT confirms the capacity of these cells to synthesize this glycoprotein [13, 29]. Further analysis of our results showed that fibronectin expression is more intense at the epithelial–mesenchymal interface of both solid ameloblastomas and AOT, showing a linear and discontinuous distribution in most cases, a fact also reported by Heikinheimo et al. [28].

A strong immunoreactivity to fibronectin was observed at the epithelial–mesenchymal interface of plexiform and follicular areas of solid ameloblastomas. Such distribution of fibronectin is probably related to the characteristics of the cells at the periphery of tumor cords and nests, which exhibit a tall columnar morphology, palisaded arrangement, and inverted nuclear polarization. In general, these cells present hyperchromatic nuclei and vacuolated cytoplasm resembling pre-ameloblasts. Desmoplastic ameloblastomas did not show expression of fibronectin at the basement membrane region, a fact that might be related to the lack of similarities between pre-ameloblasts and the peripheral epithelial cells of desmoplastic ameloblastomas [5, 31].

Andrade et al. [32] verified strong immunoexpression of $\alpha5\beta1$ integrin at the epithelial–mesenchymal interface of all histological subtypes of ameloblastoma. Integrin $\alpha5\beta1$ is the classic receptor for fibronectin [17, 24]. The binding of integrin $\alpha5\beta1$ to fibronectin plays a crucial role in the migration of neoplastic cells and is capable of increasing the expression and secretion of matrix metalloproteinases [32, 33]. Therefore, $\alpha5\beta1$ integrin has been implicated as an important molecule for the local invasiveness of ameloblastoma [32].

In the present study, no expression of fibronectin was observed in the basement membrane region of desmoplastic ameloblastomas. Despite the classification of desmoplastic ameloblastoma as a distinct subtype of ameloblastoma [1], the biological behavior of this variant is not fully understood [34]. Due to the absence of fibronectin in the basement membrane region of desmoplastic ameloblastoma, integrin $\alpha5\beta1$ cannot bind to this glycoprotein. Therefore, migration of neoplastic cells and expression and secretion of matrix metalloproteinases would be affected in this subtype of ameloblastoma.

Tenascin was frequently detected in the stroma of ameloblastomas, particularly in areas close to the epithelial–mesenchymal interface. These results suggest a possible role for this protein in the interactions between tumor cells and adjacent stroma [11]. In agreement with the reports of Murata et al. [30], AOT showed tenascin expression in the tumor stroma, with a strong perivascular labeling. However, in the present study, while the expression of this protein was intense in most cases of ameloblastoma, in AOT this expression was weaker, with large areas showing no labeling at all.

Both types of tumor showed linear and discontinuous expression of tenascin in the basement membrane region which, however, was more expressive in solid and desmoplastic ameloblastomas, in contrast to the findings of Mori et al. [11]. The high expression of tenascin in ameloblastomas, especially close to the epithelial–mesenchymal interface, might suggest a strong interaction between parenchyma and stroma in order to create a microenvironment permissive to the high proliferative activity and invasive capacity of tumor cells. This suggestion is based on the already established role of tenascin in epithelial–mesenchymal interactions during embryogenesis and development of several pathological processes [14, 16, 18, 24].

The present results also showed an intense immunolabeling for tenascin within epithelial islands of solid ameloblastomas, particularly in areas resembling stellate reticulum and in areas of cystic degeneration. These findings raise the possibility that this glycoprotein would be associated with the initial formation of cystic spaces or cavitations frequently observed inside tumor nests of follicular areas of solid ameloblastomas [11]. We believe that the sum of the growth potential of these microcysts might contribute to the elevated growth potential and the consequent markedly aggressive nature reported for most multicystic ameloblastomas.

With respect to the expression of type I collagen, both ameloblastomas and AOT disclosed a moderate to intense, diffuse distribution of this protein in the tumor stroma. In comparison with solid ameloblastomas, AOT showed a more intense type I collagen labeling, probably due to the presence of a dense and mature fibrous capsule that corresponds to a structurally, well-organized and stable connective tissue [23, 35]. The less expressive immunolabeling for type I collagen in solid ameloblastomas could be related to the presence of tumor cell-induced metalloproteinases [22] in tumor stroma, which can reduce the amount of this protein.

The distribution of type I collagen in the stroma of desmoplastic ameloblastomas was similar to that verified in AOT, and probably reflects the greater collagenization of these tumors [5]. Takata et al. [36] verified a high expression of transforming growth factor beta (TGF-β) in desmoplastic ameloblastomas. TGF-β stimulates various cells, including fibroblasts, to synthesize ECM, such as collagen, fibronectin, and proteoglycans [36]. Therefore, TGF-β may be important for desmoplastic matrix formation [36].

The analysis of the immunoexpression of type I collagen and fibronectin disclosed a distinct composition of the ECM in desmoplastic ameloblastomas. Taken together, our results might suggest a less invasive behavior of desmoplastic ameloblastomas in comparison to solid ameloblastomas. In view of the few number of hybrid lesions in our research and the absence of tumors composed only by the desmoplastic pattern, further studies comparing desmoplastic ameloblastomas, solid ameloblastomas, and hybrid lesions are necessary in order to clarify the existence of a different biological behavior between these lesions.

Immunoexpression of type I collagen in AOT was also observed in focal areas inside some duct-like structures, or in the form of irregular aggregates permeating epithelial cells organized in solid nests or whirls. According to Murata et al. [30] and based on various experiments, the different types of ECM associated with AOT, either as luminal content of duct-like structures or in the form of hyaline droplets, consist of various forms of matrix containing collagen fibrils and their degradation products.

In summary, the variations observed in the immunoexpression of the proteins studied suggest a more locally invasive behavior of ameloblastomas compared to AOT. Moreover, our results might suggest a less invasive behavior in desmoplastic ameloblastoma. The present study demonstrated the expression of fibronectin, tenascin and type I collagen in ameloblastomas and AOT, but further investigations are necessary to identify other ECM components involved in the different cellular mechanisms determining the development of tumors and thus influencing their biological behavior.

Conflict of interest statement We inform that we do not have a financial relationship with the organization that sponsored the research.

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