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Expression of integrin subunits α2, α3, α5, αv, β1, β3 and β4 in different histological types of ameloblastoma compared with dental germ, dental lamina and adult lining epithelium

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OBJECTIVE: To analyze integrin expression and distribution in different histological types of ameloblastoma, compared with dental germ, dental lamina and adult lining epithelium.

MATERIALS AND METHODS: Three-micrometer sections from paraffin-embedded specimens were evaluated employing a streptavidin–biotin immunohistochemical method and anti-integrin α2, α3, α5, αv, β1, β3 and β4 antibodies.

RESULTS: All integrins were present in all specimens, exhibiting different patterns. In follicular ameloblastoma, the integrin staining was stronger in the periphery while integrin α2 was not present in the central cells. Acanthomatous ameloblastoma showed a similar pattern, with positive staining for integrins α3, α5, αv, β1 and β4 in the metaplastic cells. In the unicystic, integrin staining was uniform except for integrins α5 and β3 which showed weaker staining in the upper layers. In the plexiform ameloblastoma, dental germ and lamina integrin staining was uniform. In the adult lining epithelium, staining for integrins α2, α5 and β4 was confined to the basal layer, while integrins αv and β3 were present in the basal and parabasal, with integrins α3 and β1 in the upper layers.

CONCLUSION: Acanthomatous, follicular and unicystic ameloblastomas showed integrin staining patterns similar to the adult lining epithelium while the plexiform ameloblastoma was similar to the dental germ and lamina.

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Keywords: integrins; ameloblastoma; dental germ; dental lamina; immunohistochemistry

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Introduction

Ameloblastoma, the most common odontogenic tumor of the jawbones (Sciubba *et al*, 1999), is a benign but locally invasive neoplasm of epithelial odontogenic origin, with a strong tendency to recur (Salo *et al*, 1999). This tumor type constitutes approximately 1% of all cysts and tumors of the jaws (Small and Waldron, 1955) and represents around 0.7% of all oral lesions received by the Surgical Pathology Service of the School of Dentistry of the University of São Paulo (Araújo and Araújo, 1984).

Three clinical types are described to ameloblastoma: solid, unicystic and peripheral (Waldron, 2002). Histologically, the solid type can be subdivided into the follicular, acanthomatous, plexiform, granular cell, desmoplasic and basal cell types. All are essentially formed by islands of epithelium resembling enamel organ epithelium, embedded in a mature, fibrous, connective tissue stroma (Waldron, 2002).

Many studies have focused on the immunohistochemical analysis of cytoskeletal components of ameloblastoma (Gao *et al*, 1989; Heikinheimo *et al*, 1989; Crivelini *et al*, 2003), and on those of the extracellular matrix (Yoshiba *et al*, 1998; Salo *et al*, 1999). However, many of the morphological and behavioral features of neoplastic cells may result from changes in adhesion molecule expression and/or function (Ohene-Abuakwa and Pignatelli, 2000). It has been proposed that integrins constitute an important component in the organization and tension of the cytoskeleton and, that in turn, strongly influence intracellular phenomena like cell proliferation and differentiation (Ingber, 1997). Despite this, to the best of our knowledge, there are no studies dedicated to clear up the role of integrins – one of the most important adhesion molecules – in the behavior of odontogenic tumors.

Integrins are a major family of adhesion receptors that bind to both cell surface and extracellular matrix

ligands (Humphries and Newham, 1998; Gonzalez-Amaro and Sanchez-Madrid, 1999). They are heterodimeric molecules, constituted by an α and a β subunit, both of which are type-1 transmembrane glycoproteins. Currently, 16 α and eight β subunits have been identified in humans, and these may unite, through non-covalent bonds, in a restricted manner, to form 22 different dimers, each of which exhibits a different ligand-binding profile (Humphries and Newham, 1998). Owing to their number and complexity, the integrins are further divided into subgroups based on their β subunits (Andreoli, 1999).

Thus, integrin engagement activates multiple downstream molecules necessary for cell survival. Disengagement of integrin-mediated adhesion to the extracellular matrix is required for cellular translocation and invasion, and neoplastic cells, frequently showing disturbed integrin expression, resulting in aberrant morphology and behavior, have been identified (Liotta and Kohn, 2001). In the present study, we analyze the distribution and expression of integrins $\alpha2$, $\alpha3$, $\alpha5$, αv, $\beta1$, $\beta3$ and $\beta4$ in the follicular, acanthomatous, plexiform and unicystic histological types of ameloblastoma by immunohistochemistry, and compare these findings with dental germ, lamina and adult lining epithelium.

Materials and methods

Based on the latest World Health Organization classification of odontogenic tumors, 14 cases of ameloblastoma, including four of the follicular subtype, six of the plexiform subtype, two of the acanthomatous subtype, and two of the unicystic subtype; four of dental germ and lamina; and one case of normal mucosa, were retrieved from the archives of the Oral Pathology Department of the School of Dentistry of the University of São Paulo (São Paulo, Brazil).

For morphological analysis, 5 μm sections were obtained from formalin-fixed paraffin embedded samples and routinely stained with hematoxylin–eosin.

Three-micrometer sections from these specimens were deparaffinized, rehydrated and submitted to antigen retrieval in 0.5% pepsin pH 1.8 for 30 min at 37°C. The specimens were then incubated in 3% aqueous hydrogen peroxide for 30 min to quench endogenous peroxidase activity. Incubation with 1% BSA and 5% fetal calf serum in Tris–HCl, pH 7.4 for 60 min at room temperature was performed to suppress non-specific binding of subsequent reagents. The sections were then incubated with the primary anti-integrin antibodies $\alpha2$, $\alpha3$, $\alpha5$, αv, $\beta1$, $\beta3$ and $\beta4$ (Chemicon, Temecula, CA, USA) overnight diluted 1:1500. The antibody-binding detection system 'catalized signal amplification system' (CSA system, HRP, Dako, Carpinteria, CA, USA), was then employed consisting of sequential 15-min incubations with biotinylated link, streptavidin complex, amplification reagent and streptavidin peroxidase (steps 4–9 of the Dako CSA System, HRP). Each of these 15-min incubation steps were preceded by a 5-min rinse with 1% Tween 20 Tris–HCl, pH 7.4. Staining was completed by 3-min incubation with 3′-3-diaminobenzidine tetrachloride (DAB; Sigma, St Louis, MO, USA), which resulted in a brown colored precipitate at antigen sites. The specimens were then lightly counterstained with Mayer's hematoxylin, dehydrated and mounted with glass coverslips and xylene-based mountant.

Negative controls were treated as above, but a solution of 1% BSA in Tris–HCl, pH 7.4 replaced the primary antibody. The epithelium and blood vessels were considered as internal positive controls.

Results

Results are summarized in Table 1.

Ameloblastoma

In the follicular subtype, islands of epithelium resembling the enamel organ were seen embedded in a mature, fibrous, connective tissue stroma. The epithelial nests consisted of a central core of loosely arranged, angular cells resembling the stellate reticulum, surrounded by a single layer of tall, columnar, ameloblast-like cells. All integrins were expressed strongly in the peripheral cells of the epithelial islands, revealing a reticular pattern of staining, mainly concentrated at the basal pole of these cells. In the central cells, with the exception of integrin $\alpha2$ for which staining was negative (Figure 1b), expression was weaker, with a regular distribution throughout the cytoplasm, although in same cells a reticular staining pattern was seen (Figure 1a).

The acanthomatous subtype was represented by a squamous metaplasia present in the central regions of the epithelial islands of the follicular ameloblastoma. Integrin distribution was very similar to that seen in the follicular subtype, although the β integrins were less prominent in the peripheral cells. Metaplastic cells in the central areas of the islets expressed integrins $\alpha3$, $\alpha5$, αv, $\beta1$ and $\beta4$ (Figure 1c) and not integrins $\alpha2$ and $\beta3$ (Figure 1d).

The plexiform type of ameloblastoma was represented by long, anastomosing cords or larger sheets of odontogenic epithelium. These structures were bounded by columnar or cuboidal ameloblast-like cells surrounding more loosely arranged epithelial cells. The supporting stroma was loosely arranged and vascular. Staining for all integrins was strongly positive, showing a reticular pattern, with a regular distribution throughout the cytoplasm (Figure 1e). The central cells showed a slightly weaker expression of integrin $\beta3$ (Figure 1f).

Both unicystic ameloblastomas examined were of the luminal variant. Histologically, they consisted of a fibrous cyst wall with a lining that was represented by odontogenic epithelium whose basal layer consisted of columnar cells with hyperchromatic nuclei showing reverse polarity; the overlying epithelial cells were loosely cohesive and resemble the stellate reticulum. All integrins were expressed in the cells of the basal layer, revealing a reticular staining pattern, and were mainly concentrated at the basal pole of these cells. In the upper layers, expression in the cytoplasm was more regular in distribution (Figure 1g). Integrins $\alpha5$ and $\beta3$ showed a weaker expression in the upper layers (Figure 1h).

Table 1 Intensity of immunostaining for integrins in ameloblastoma, dental germ, dental lamina and adult lining epithelium

	α2	*α3*	*α5*	*αv*	*β1*	*β3*	*β4*
Follicular ameloblastoma							
Peripheral cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Central cells	–	+	+	+	+	+	+
Acanthomatous ameloblastoma							
Peripheral cells	+ + +	+ + +	+ + +	+ + +	+ +	+ +	+ +
Central cells	–	–	–	–	–	+	–
Metaplastic cells	–	+	+	+	+	–	+
Plexiform ameloblastoma							
Peripheral cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Central cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +
Unicystic ameloblastoma							
Basal layer cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Upper layers cells	+ + +	+ + +	+	+ + +	+ + +	+	+ + +
Dental germ							
Epithelial structures	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Dental papilla	–	–	–	–	–	–	–
Dental lamina							
Peripheral cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Central cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +
Adult lining epithelium							
Basal layer cells	+	+	+	+	+	+	+
Parabasal layer cells	–	+	–	+	+	+	–
Upper layers	–	+ + +	–	–	+ + +	–	–

+, Weak staining; + +, moderate staining; + + +, strong staining; –, negative staining.

Dental germ
The dental germ analyzed was in the bell stage of development. The pattern of integrin staining was strongly positive and reticular, and all layers of the enamel organ were positive. Immunostaining in the inner dental epithelium was concentrated at the basal pole of the cells. The dental papilla was completely negative (Figure 2a).

Dental lamina
The pattern of integrin distribution was strongly positive and reticular, being located at the basal pole of the peripheral cells, and throughout the cytoplasm of the central cells (Figure 2b).

Adult lining epithelium
Integrins α2, α5 and β4 showed faint expression restricted to the basal layer (Figure 2d). Integrins αv and β3 showed the same pattern, but were localized in the basal and parabasal layers. Integrins α3 and β1 were strongly positive in the upper layers, and faint in the basal and parabasal layers (Figure 2c).

Discussion

Recent studies have revealed a pivotal role for integrins in the development and homeostasis of multicellular organisms (Gonzalez-Amaro and Sanchez-Madrid, 1999), and in the regulation of survival, proliferation and invasion by tumoral cells (Varner and Cheresh, 1996).

In the present study, we detected immunohistochemically the presence of different integrins in the ameloblastoma, and compared these findings with the dental germ, dental lamina and normal mucosa epithelium.

In general, all the integrins studied in the different ameloblastomas stained positively, with variations detected in distribution and staining intensity.

The pattern exhibited by the follicular ameloblastoma was a strong staining in the peripheral layer of the neoplastic follicles, localized mainly at the basal pole of the cells, plus faint staining in the central layers, except for integrin α2 that was expressed only in the peripheral cells. These features suggest an important role for integrins in the cell–basal membrane interaction.

It is well known that the conjugated integrin α2β1, a receptor for collagen and laminin (Zutter *et al*, 1995), inhibits the cell cycle and promotes matrix remodeling by increasing both collagen synthesis and degradation (Langholz *et al*, 1995; Riikonen *et al*, 1995; Koyama *et al*, 1996; Ivaska *et al*, 1999; Heino, 2000). This integrin binds to collagen through αI – an α2 domain (Tulla *et al*, 2001) and its ectopic expression suppresses the growth of breast carcinoma cells and induces their differentiation (Zutter and Santoro, 1990). As a laminin receptor, expression of this conjugated integrin by tumors has been well investigated, due to its role in regulating basement membrane assembly and subsequent correlation with invasive potential (Miller and Veale, 2001). The conjugated integrin α2β1 expression is decreased in oral squamous cell carcinoma (Sugiyama *et al*, 1993), endometrial cancer with lymph node metastasis (Lessey *et al*, 1995), invasive breast cancer (Van Valen *et al*, 1994) and gastric carcinoma (Koike *et al*, 1997). However, it is increased in prostatic cancer cell lines (Haywood-Reid *et al*, 1997), in pancreatic cancer (Weinel *et al*, 1992) and in invasive melanoma (Vink *et al*, 1993). Thus, the discrete decrease in the expression of α2 seen in the ameloblastoma compared to the dental lamina and dental germ, may be related to the

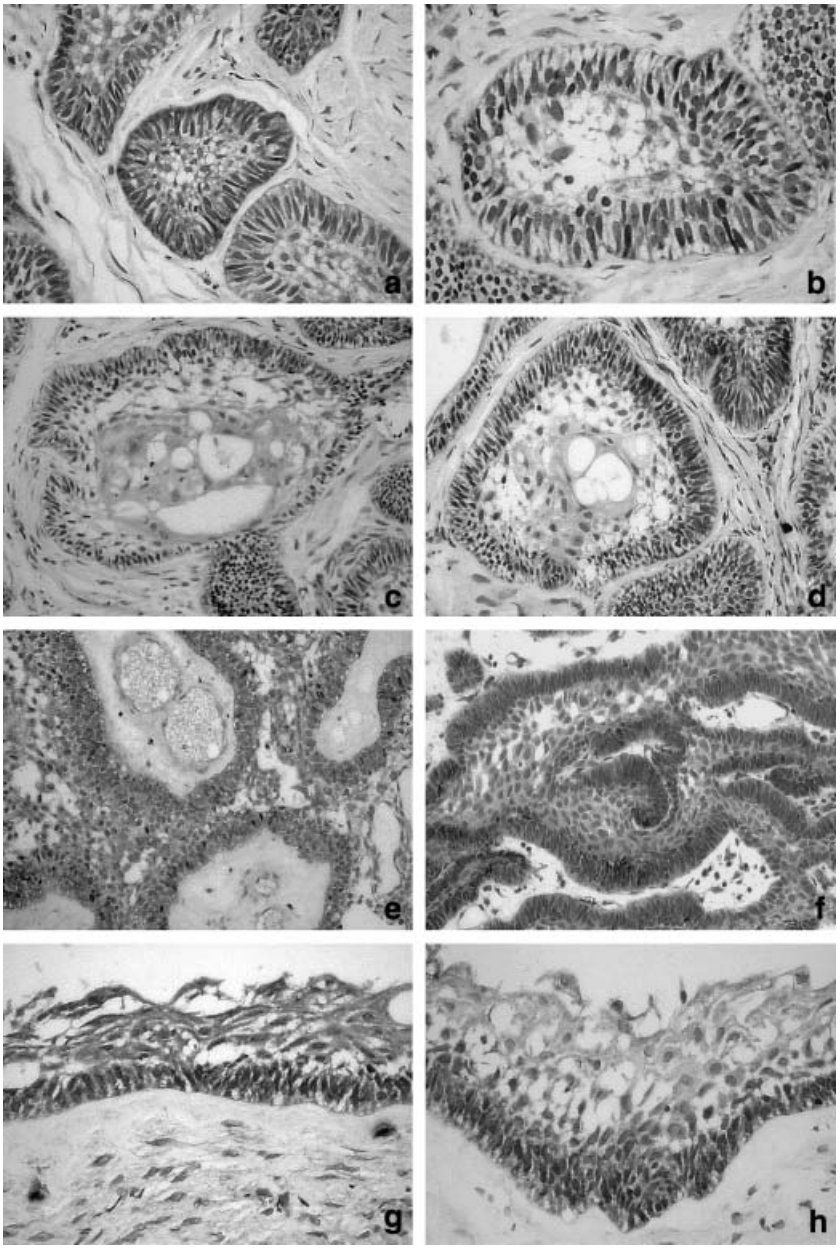

Figure 1 Integrin immunostaining in different types of ameloblastoma. Streptavidin–biotin. (**a**) Follicular ameloblastoma: intense staining for integrin $\alpha 3$ in the periphery, and fainter expression in the center of the tumoral islands (100× in the original). (**b**) Follicular: integrin $\alpha 2$ staining is positive in the peripheral cells and absent from the central cells of the islands (200×). (**c**) Acanthomatous: metaplastic cells in the center of the islands positive for integrin $\alpha 3$. Peripheral cells are also strongly positive (100×). (**d**) Acanthomatous: metaplastic cells negative for integrin $\beta 3$ (100×). (**e**) Plexiform: intense staining for integrin $\alpha 3$ in all neoplastic cells (100×). (**f**) Plexiform: intense staining for integrin $\beta 3$ in peripheral cells and slightly weaker expression in central cells (100×). (**g**) Unicystic: regular staining for integrin αv in all layers (200×). (**h**) Unicystic: integrin $\alpha 5$ shows stronger staining in the basal layer compared to the upper layers (200×)

growth and invasion of the contiguous tissues characteristic of this lesion.

In the same manner, the expression of integrin $\beta 1$ in ameloblastomas was also slightly decreased compared with its expression in dental germ and dental lamina. It is known that integrin $\beta 1$ – through its $\beta 1$C unit, which prevents cell cycle progression – plays a direct role in proliferation control and cell differentiation (Meradith *et al*, 1995). Decreased levels of $\beta 1$ have been correlated with anchorage independent growth (Suzuki and Takahashi, 1999).

The acanthomatous ameloblastoma showed positive staining in the metaplastic cells for integrins $\alpha 3$, $\alpha 5$, αv, $\beta 1$ and $\beta 4$, while integrin $\beta 3$ was expressed in the stellate cells and integrin $\alpha 2$ was negative in both. The pattern of squamous metaplastic areas was similar to that for the adult lining epithelium, with the exception of integrins $\alpha 5$, αv and $\beta 4$, neither of which were expressed in this tissue.

The plexiform ameloblastoma showed a strong presence of all integrins studied in its structures. This expression resembles that seen in the dental lamina and dental germ.

In the unicystic ameloblastoma, all the integrins were strongly positive in the basal layer. The upper layers also stained strongly for integrins, with the exception of integrins $\alpha 5$ and $\beta 3$. This pattern is similar to that seen in the adult lining epithelium, especially the decreased expression of integrins $\alpha 5$ and $\beta 3$ in upper layers. The conjugated integrin $\alpha v \beta 3$ has been implicated as the main binding protein to the cytoskeleton, and as an anchor for important components of various transduction systems (Sastry and Horwitz, 1993).

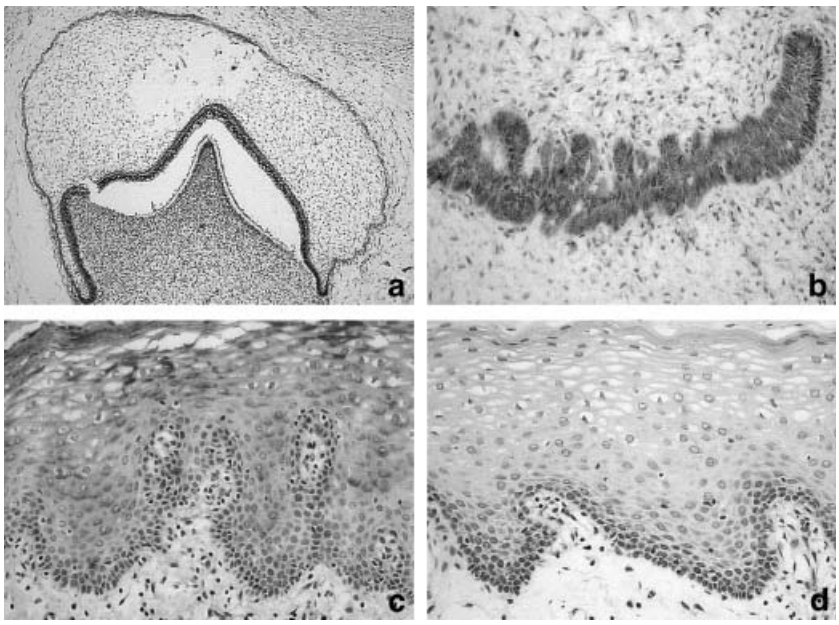

Figure 2 Streptavidin–biotin. (**a**) Integrin $\alpha 5$ staining in the dental germ showing weak positivity in all cells of the enamel organ, and absence from the dental papilla (25×). (**b**) Strong staining for integrin $\beta 1$, concentrated at the basal pole of the peripheral cells and throughout the cytoplasm of the central cells, in the dental lamina (100×). (**c**) Cells of the upper layers of the adult lining epithelium showing stronger integrin $\beta 1$ staining compared to cells of the basal and parabasal layers (100×). (**d**) Weak integrin $\beta 4$ staining restricted to cells of the basal layer (100×)

The abundant presence of integrin αv in ameloblastoma neoplastic cells, including all layers of unicystic ameloblastoma, deserves special attention, as this integrin may be related to their proliferative and invasive nature. Integrin αv positively regulates tumoral cell proliferation (Felding-Habermann *et al*, 1992). Ectopic expression of $\alpha v\beta 5$ by oral squamous cell carcinoma has been linked to failure of normal cell differentiation, while ectopic expression of $\alpha v\beta 6$ has been linked to promotion of proliferation (Jones *et al*, 1997), although in melanomas $\alpha v\beta 3$ blockage may inhibit tumor progression (Natali *et al*, 1997). The expression of integrin αv by neoplastic cells permits adhesion and mediation of migration by a large repertoire of ligands, which may be advantageous during invasion (Marshall and Hart, 1996).

It is important to observe the weak staining for integrin $\alpha 5$ in the inner layers of the follicular subtype, in the upper layers of the unicystic ameloblastoma, and negative staining in the stellate cells of the acanthomatous subtype. Similarly, the normal adult lining epithelium showed negative staining for integrin $\alpha 5$ in parabasal and upper layers. Therefore, the distribution of integrin $\alpha 5$ in follicular, acanthomatous and unicystic ameloblastoma subtypes resembles its distribution in the adult lining epithelium.

An emerging trend in epithelial tumors is the influence of integrin expression in unregulated growth (Ziober *et al*, 1996) and invasion, an important feature of ameloblastoma. It is known that neoplastic cells may have a modified repertoire of integrins, which may enable them to regulate adhesive and anti-adhesive events (Marshall and Hart, 1996) and tumor development (Meyer and Hart, 1998).

Less mature tissues showed positivity for integrins in most of their cells, differently from the adult lining epithelium. This suggests that integrins play a key role in tissue development, an assertion that deserves further investigation.

In general, the expression of integrins in follicular, acanthomatous and unicystic ameloblastoma subtypes, was as intense as its occurrence in development tissues (i.e. dental germ and lamina), although with a distribution similar to the lining adult epithelium. Further, the pattern of integrin staining in the plexiform subtype was similar to that seen in embryonic tissues (developmental structures).

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