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Original Article

Downregulation of connexin 43 is crucial for basal cell alignment in ameloblastoma and odontogenic keratocyst

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ABSTRACT

Background: The current study aims at investigating gap junctions which allow cells to connect with one another. Such process is essential for cell differentiation and the preservation of diverse cell functions. It is noticeable that connexin 43 (Cnx43) was differentially expressed in ameloblasts and odontoblasts in the processes of odontogenesis. Moreover, in carcinoma in situ (CIS) and oral squamous cell carcinoma (SCC), Cnx43 expression apparently thought to be a defining feature of the neoplastic state of squamous epithelial cells. *Aim*: Therefore, the study has postulated that Cnx43 may be involved in the pathophysiology of ameloblastoma and certain odontogenic cysts whose epithelial constituents exhibit squamous cells.
Materials and methods: In order to prove the foregoing hypothesis, the study explored the immunohistochemical profiles of Cnx43 in ameloblastoma as well as some odontogenic cysts to assess Cnx43 trafficking and its relation with characteristic tissue architectures of odontogenic lesions. *Results*: The study has concluded that Cnx43 was down regulated significantly in follicular ameloblastoma with obvious ameloblasts-like cell components as well as in odontogenic keratocyst with palisaded basal cells. Additionally, other patterns of ameloblastoma (plexiform and desmoplastic) and different types of odontogenic cysts manifest heavy trafficking for Cnx43. *Conclusion*: Finally, altered Cnx43 expression between various patterns of ameloblastoma and odontogenic cysts might be related to their pathogenesis and is responsible for their morphological diversity.

1. Introduction

Generally speaking, odontogenic lesions are classified according to the tissue from which they originate. They stem from the epithelial and/or ectomesenchymal components involved in the odontogenesis process. Tumors originating from the odontogenic apparatus, its derived structures, or the residual of the system giving rise to different diseases exhibit histologic diversity. Ameloblastomas are among the most common benign neoplasms arising from odontogenic epithelium. They are distinguished by their slow pattern of growth, localized infiltration, and a notable propensity for recurrence. These tumors share similar features: physical similarities with odontogenic epithelial tissue features, including the dental lamina and/or enamel organ (Soluk-Tekkesin and Wright, 2022).

Gap junction channels are produced by a membrane protein called connexin 43 (Cnx43). These channels mediate intercellular transport as well as intracellular signaling. Its rapid synthesis, brief half-life, and efficient transit are necessary for maintaining intracellular combination and gap junction cellular organization. Gap junction trafficking impairment is a contributing factor to dangerous consequences (Delmar et al., 2018). Remarkably, Silveira et al., 2023 inspected Cnx43 expression in odontogenic tissues and specified that it has crucial role in mineralization procedure.

Neonate rats' developing tooth germs contain Cnx43 in both mesenchymal and epithelial dental cells. It's also been discovered in the areas that exist between ameloblasts and odontoblasts. The expression of Cnx43 gradually enhanced as a preodontoblast matures (Yamada et al., 2021). Prior to enamel production, Cnx43 expression varies amongst late pre-secretory ameloblasts and increases in size as the secretory stage of ameloblast development advances. Cnx43 facilitates the maturation stage of enamel synthesis by allowing ions to be transferred to ameloblasts. Human dental follicle cells regularly express Cnx43 at high levels after tooth germ formation is complete, which is assumed to be necessary for tooth eruption. These findings suggest that Cnxs play a function in tooth development which is a complex process, and it is plausible that distinct subtypes of connexins (Cnxs) could potentially fulfill diverse functions in odontogenesis and tooth homoeostasis (Al-Ansari et al., 2018; Yamada et al., 2016).

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Connexins have been explored in the human gingival epithelium, where Cnx43 even forms plaques in fibroblasts and Cnx26 and Cnx43 are frequently expressed at high levels by keratinocytes. During the mineralization processes, Cnx43 expression is upregulated in cultured human pulp cells, indicating a possible role for Cnx43 in mineralization (Chiba et al., 2020).

Hence, the study suggests a hypothesis in light of all the collected data on Cnx43′s function in the development of odontogenic tissues: Cnx43 trafficking may enhance the morphological diversity and architecture of ameloblastomas and odontogenic cysts, and it may even be involved in basal cell alignment.

2. Material and methods

2.1. Samples

The current study was conducted on 58 paraffin blocks listed as (42) ameloblastomas, (8) odontogenic keratocysts and (8) radicular cysts. Histopathological variants of ameloblsatoma were used; follicular (19); plexiform (13); desmoplastic (5) and unicystic ameloblastoma (5). The sample calculation is determined using software (N-master), taking into consideration the prevalence of diseases. This calculation is founded upon a pilot study conducted beforehand. Blocks were collected from the archived files of patients at Faculty of Dentistry, Oral Pathology Department, Tanta University. 5 μm paraffin blocks successive sections were cut for immunohistochemistry and H&E staining.

The design and procedures of the present study were performed in agreement with the research guidelines of Ethical Research Committee, University of Tanta, Faculty of Dentistry. Paraffin-embedded tissue blocks record were gotten from Faculty of Dentistry, Oral Pathology Department, Tanta University after taking a written approval from the head of the Oral Pathology Department.

2.2. Antibodies

Polyclonal antibodies (Rabbit) for connexin 43 (Cnx43) (GJA1) were acquired from Abcam (UK)

2.3. Immunohistochemistry

Immunohistochemical labeling was carried out in successive slices utilizing the ChemMate Envision system (Dako) (Essa and Deraz, 2022). In short, a succession of graded alcohols was used to rehydrate tissue slices that had undergone deparaffinization. Then, endogenous peroxidase activity was inhibited for 30 min at room temperature using 0.003 % hydrogen peroxide in methanol. Sections were washed in 0.01 M saline (phosphate-buffered) (PBS, pH 7.4). The sections for Cnx43 were autoclaved at 121 °C for 10 min in buffer of citrate (pH 6.0). Then, sections were incubated for 1 h at 37 °C in 0.01 M PBS comprising 0.05 % Triton X-100 and 5 % milk protein (Morinaga Milk Industry Co. Ltd, Tokyo) to prevent non-specific protein binding locations. The sections were then incubated for an additional night at fridge with suitably Cnx43 diluted at 1:100. The sections were then rinsed with PBS and allowed to sit at room temperature for 60 min while the Envision reagents were incubated. To get the reaction results, 0.02 % 3,3′-diaminobenzidine in 0.05 M Tris-HCl buffer (pH 7.6) containing 0.005 % hydrogen peroxide were added to slides. Hematoxylin was used as a counterstain. Pre-immune IgGs (mouse or rabbit) were used as a replacement for of the primary antibodies in order to perform control experiments on antibodies.

2.4. Assessment of results of immunohistochemistry

The assessment of Cnx43 staining was conducted by two impartial observers who possessed commensurate expertise and held equivalent positions (academic), yielding a consensus between their findings. Subsequently, tissue sections were revealed at a lower level of magnification, three fields were randomly chosen at a higher level of magnification using an objective lens (40 ×). These selected fields, viewed as representative of the specimens, were captured in photographs using Nikon Eclipse microscope armed with a Nikon DXM1200C digital camera (Japan). Cnx43 positive expression was determined by the presence of immunoreactivity in the cytoplasm and/or membrane. Mononucleated cells that tested positive for Cnx43 were manually counted in 0.25 × 0.25 mm a unit field on serial sections. The results of immunostaining were assessed according to the grading system described by Bencze et al., 2021. Positive tumor cell percentage was divided into the resulting groups: grade 0 for none or no expression, then grade 1 for 1 to 25 % cells are positive, grade 2 for 26 to 50 % positive cells, grade 3 for 51 to 75 % positive cells, and grade 4 for 76 to 100 % positive cells. Immunostaining intensity was rated as follows: none (0), weak (1), moderate (2), and strong (3). Specimens were positive when more than one percent of cells exhibited strong sign of staining (Bencze et al., 2021).

2.5. Statistical processing

The collected data for this study was collated, compiled, and statistically processed utilizing “SPSS 20” (Statistical Package for the Social Sciences) (SPSS Inc., Chicago, Illinois, USA) “SPSS 20”. The significance level was evaluated by employing probability rate of 0.05.

3. Results

3.1. Cnx43 expression in different ameloblastoma types

Follicular type ameloblastoma presents as ameloblast-like tall columnar cells with reverse polarity; in the center, there are polygonal cells with nearby fibrous connective tissue (Fig. 1A). Plexiform type denotes the absence of differentiation between central and peripheral cells into tall columnar and stellate cells, as well as the connective tissue that lies between (Fig. 1B). Desmoplastic type exhibits extensive fibrous connective tissue between squamous epithelial-like peripheral and central cells (Fig. 1C). Cnx43 only expresses as a dot pattern in central cells of follicular ameloblastoma and is not expressed at all in peripheral palisaded ameloblast-like cells (Fig. 1D). In plexiform ameloblastoma, Cnx43 is expressed in a dotlike pattern in both peripheral as well as central cells (Fig. 1E). In desmoplastic type, every cell expresses Cnx43 in a membrane-like manner (Fig. 1F) (Table 1).

3.2. Cnx43 expression in different types of odontogenic cysts

A parakeratinized epithelial lining, palisading tall columnar basal cells, suprabasal cells, and a connective tissue wall comprise the odontogenic keratocyst in several odontogenic cyst instances (Fig. 2A). Unicystic ameloblastoma exhibiting suprabasal stellate reticulum-like cells and basal palisading ameloblast-like tall columnar cells with reverse polarity (Fig. 2B). A radicular cyst with cells that have not differentiated into basal and suprabasal cells and an epithelial lining (Fig. 2C). Only suprabasal cells express Cnx43 in a dot-like pattern; all peripheral palisaded cells and peripheral parakeratin layer cells do not express Cnx43 at all (Fig. 2D). Cnx43 is wholly not expressed in all peripheral palisaded ameloblast like cells and only expressed in a dot-like pattern in suprabasal cells (Fig. 2E). In the epithelial lining of radicular cyst, Cnx43 in expressed in all cells in a dot like pattern (Fig. 2F) (Table 1).

4. Discussion

As far as we are aware, first study is this to review the differential disclose of connexin 43 in some odontogenic cysts and ameloblastomas. The most significant and practically useful finding of the study was that, in contrast to other cells in the remaining types of ameloblastoma and

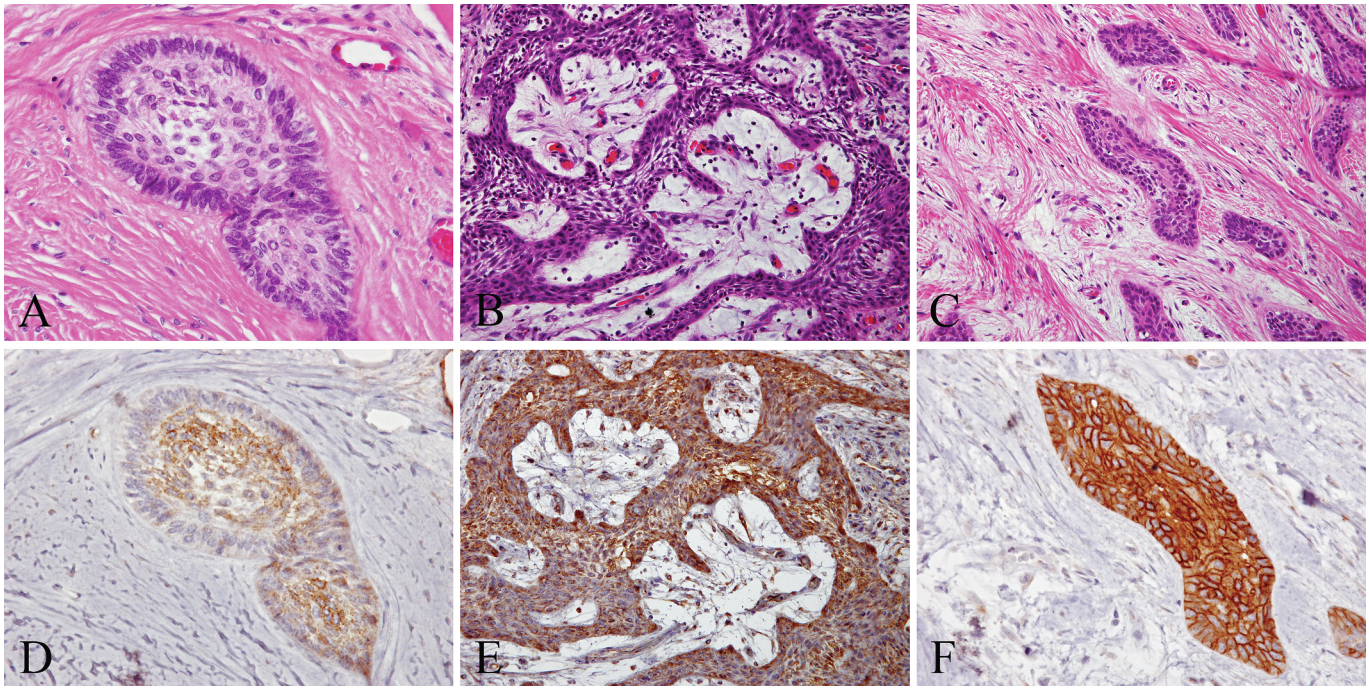

Fig. 1. A photomicrograph of H&E stained tissue sections exhibit different types of ameloblastoma; follicular type with peripheral palisading tall columnar ameloblast like cells with reverse cell polarity and central stellate reticulum like cells (A). Plexiform type with peripheral and central cells not differentiated into tall columnar and stellate cells (B). Desmoplastic type with peripheral palisading and central cells resembling squamous epithelial cells (C). Cnx43 is completely not expressed in all peripheral palisaded ameloblast like cells and only expressed in a dot like pattern in central cells (D). Cnx43 is expressed in a dot like pattern in both peripheral as well as central cells (E) In desmoplastic type, Cnx43 in expressed in all cells in a membranous pattern (F). Hematoxylin and eosin (HE) (A-C) and immunoperoxidase stains for Cnx43 (D-F)); (A, B, D-F) × 200; (C) × 100

Table 1
Cnx43 expression patterns in ameloblastomas and odontogenic cysts.

Histologic variants of Odontogenic lesions (n = 58)	Description of associated odontogenic epithelial cells	Cnx43 expression		
		Density	Pattern	Cellular Location
Ameloblastoma follicular pattern (19)	Prominent ameloblast-like cells	Not positive		
	Prominent stellate reticulm-like cells (loosely attached)	Weak	Granular	Perinuclear/ Cytoplasmic
Ameloblastoma plexiform pattern (13)	Less prominent ameloblast-like cells	Weak	Dot-like	Perinuclear/ Cytoplasmic
	Prominent stellate reticulm-like cells (loosely attached)	Weak	Dot-like	Perinuclear/ Cytoplasmic
Ameloblastoma desmoplastic pattern (5)	Firmly attached peripheral cells	Strong	Membranous	Cell border
	Firmly attached central cells	Strong	Membranous	Cell border
Unicystic ameloblastoma (5)	Less prominent ameloblast-like cells	Weak	Dot-like	Perinuclear/ Cytoplasmic
	Prominent stellate reticulm-like cells (loosely attached)	Weak	Dot-like	Perinuclear/ Cytoplasmic
Odontogenic kerstocyst (8)	Palisaded basal cells			
	Suprabasailar cells (firmly attached)	Perinuclear/ Cytoplasmic	Granular	Strong
	Superficial compacted parakeratin layer	Not positive		
Radicular cyst (8)	Basal cell layer	Weak	Dot-like	Perinuclear/ Cytoplasmic
	Suprabasailar cells (loosely attached)	Weak	Dot-like	Perinuclear/ Cytoplasmic

odontogenic cysts, where Cnx43 is diffusely expressed and exhibits enhanced trafficking pattern, Cnx43 was not expressed in ameloblast-like cells in ameloblastoma (especially follicular type) and in the basal cells of odontogenic keratocyst epithelial lining. This finding elucidates the potential role of Cnx43 in the pathophysiology of odontogenic keratocysts and ameloblastomas, and provides support for the notion that the absence of Cnx43 is linked to basal cell alignment in both conditions. More interestingly, the difference in Cnx43 expression noticed in the present study might explain the variable behavior of odontogenic lesions as well as the similarity of Cnx43 expression in the basal cells between ameloblastomas and keratocysts, explains the highly aggressive and invasive behavior of keratocyst and supports its neoplastic potential. Taken together, our findings expose the role of Cnx43 in the procedure that could control a cell's polarity encompass Cnx43 and different cytoskeleton proteins interactions.

Defects in the structures and functions of gap junction molecules, as well as those of the remaining junction molecules, are considered to be one of the primary processes in the development of epithelial neoplasms.

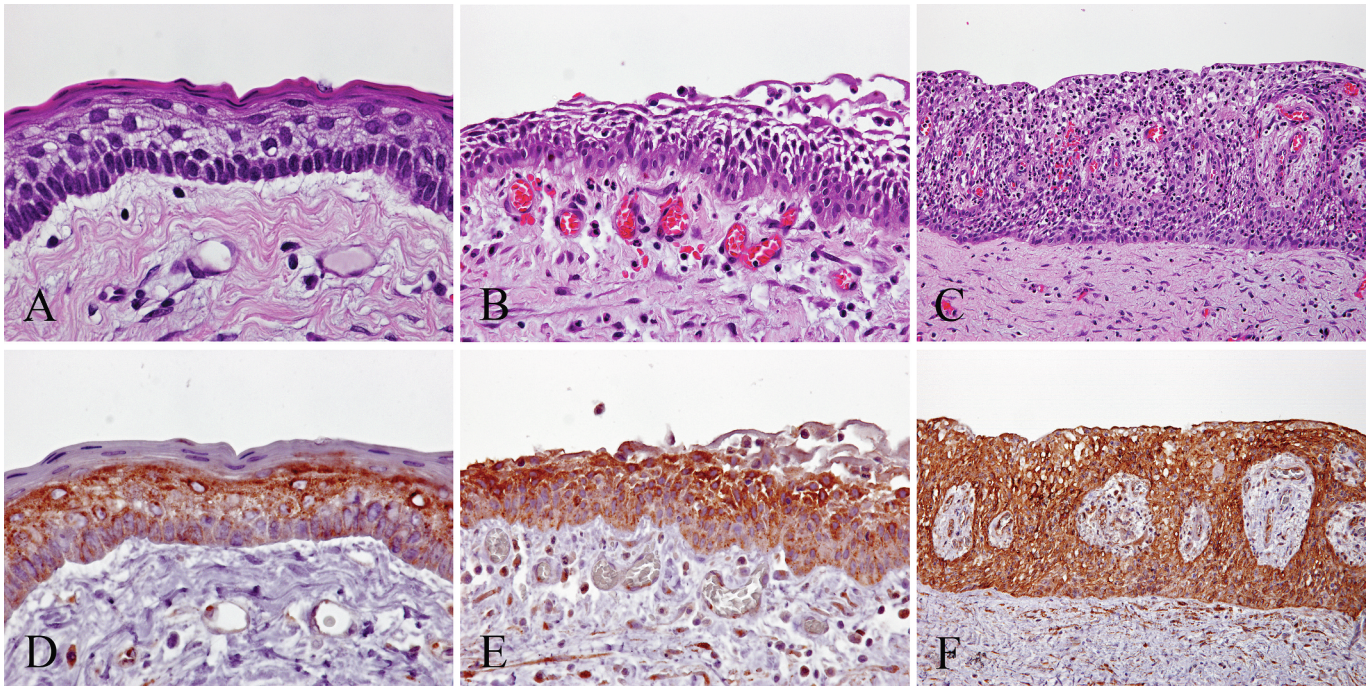

Fig. 2. A photomicrograph of H&E stained tissue sections exhibit different cases of odontogenic cysts; odontogenic keratocyst with an epithelial lining with palisading tall columnar basal cells and suprabasal cells (A). Unicystic ameloblastoma with basal palisading tall columnar ameloblast like cells with reverse cell polarity and suprabasal stellate reticulum like cells (B). Radicular cyst with an epithelial lining with cells not differentiated to basal and suprabasal cells (C). Cnx43 is completely not expressed in all peripheral palisaded cells as well as peripheral parakeratin layer and only expressed in a dot like pattern in suprabasal cells (D). Cnx43 is completely not expressed in all peripheral palisaded ameloblast like cells and only expressed in a dot like pattern in suprabasal cells (E) In the epithelial lining of radicular cyst, Cnx43 in expressed in all cells in a dot like pattern (F). Hematoxylin and eosin (HE) (A-C) and immunoperoxidase stains for Cnx43 (D-F)); (A-F) × 200.

This causes cellular cohesiveness to be disrupted, allowing nutrients and growth hormones to diffuse and increasing tumor cell proliferation, differentiation, and invasiveness sequentially (Tien et al., 2014; Obert et al., 2017).

The findings agree with those of Bazzoun et al., 2019 who linked Cnx43 to breast epithelial tissue homeostasis in tissues other than odontogenic ones. It was demonstrated that Cnx43 facilitates the maintenance of breast epithelial cells by controlling the establishment and maintenance of apical polarity, which in turn controls entry of cell cycle and orientation direction of mitotic spindle. They also emphasized the connection between the absence of Cnx43 in epithelial cells and apical polarity disruption.[12] Furthermore, alterations in the apicolateral spreading of the polarity-determinant zonula occludens-1 a tight junction molecule; results in the absence of Cnx43 due to block gap junction inter-cellular assembly (chemically induced). This leads to cell multilayering and random orientation direction of mitotic spindle (Fostok et al., 2019).

Many studies on odontogenic lesions that yielded comparable results found that the expression levels of Cnx43 and Cnx32, together with the mRNA expression levels, are greatly down-regulated in odontogenic keratocysts. Notably, they also demonstrated—and this is similar with our findings—that the expression levels of Cnx43 and Cnx32 in odontogenic keratocysts showed an inverse connection with PCNA, cyclin D1, and Bcl-2. Cnx43 is confined to granular and squamous cells in granular cell and acanthomatous ameloblastomas, respectively, but is revealed extensively in the most of odontogenic tumors (Zhong et al., 2015). While bordering columnar cells and central stellate-reticulum-like cells show significant staining, ameloblast-like cells show no-to-weak expression. Because Cnx43 is downregulated, one could be inclined to speculate that ameloblastoma and odontogenic keratocyst have the potential to become malignant (Muramatsu et al., 2013).

Altogether, the results of the study provide strong evidence that Cnx43 may contribute to the cell polarity of odontogenic lesions for the first time and imply that its downregulation may be a part of the pathophysiological mechanism of odontogenic lesions. Unlike other transmembrane proteins, connexins have an exceptionally short half-life of 1.5–5 h, following which they degrade rapidly. Connexins are normally broken down by ubiquitin-proteasomal, lysosomal, and autophagic pathways. The present study elucidates the activation of autophagy in odontogenic lesions and suggests that it may play a role in modulating Cnx43 through its degradation. This could potentially shed light on the underlying pathogenic mechanisms, leading to enhanced diagnostic capabilities and novel therapeutic approaches for odontogenic lesions (Tarzemany et al., 2015; Yin et al., 2021; Mazel, 2017).

Further investigation is required to obtain mechanistic understanding of how Cnx43 controls cell polarity and cytoskeleton dynamics. Further biochemical investigation to elucidate the potential effects of Cnx43′s interaction with other cytoskeleton proteins on their assembly and turnover will be essential. To pinpoint the precise molecular mechanism behind the interactions between autophagic proteins and connexins in odontogenic lesions, more investigation is still required (Strauss and Gourdie, 2020).

Ultimately, we discover that Cnx43 is often expressed in the odontogenic cyst and tumor epithelial cells, suggesting a potential role for Cnx43 in the local aggressiveness of odontogenic keratocysts and ameloblastomas. Furthermore, it seems from the findings that distinct Cnx43 trafficking characteristics were linked to the varied phenotypic and morphological changes in multiple odontogenic cysts and ameloblastoma.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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