Cytokeratins 14 and 19 in odontogenic cysts and tumors: a review

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Abstract

All mammal cells include a cytoplasmic fiber system essential for cell mobility, the cytoskeleton, formed by three main structural units and associated proteins: microfilaments, microtubules and intermediate filaments. Cytokeratins are intermediate filaments forming a complex network which extends from the nucleus surface to the peripheral cell sector, where they are inserted into desmosomes and hemidesmosomes. Cytokeratins 14 and 19 have been used as diagnosis and prognosis markers in various tumors of epithelial origin, not only to identify a cell as epithelial, but also to identify different stages during epithelial differentiation and to characterize the tumor. There are numerous studies in biomedical literature that have exemplified the utility of cytokeratins 14 and 19 to identify odontogenic epithelium. This review analyzes the utility of their immunologic expression in the different cysts and odontogenic tumors.

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What are cytokeratins?

All mammal cells include a cytoplasmic fiber system essential for cell mobility: the cytoskeleton. If we try to explain it in a simple and colloquial way, we could compare it to the steel rods that support the structure of a building: the cytoskeleton plays a key role as it supports the plasma membrane and presents paths along which organelles and other cytosol elements can move. However, unlike the passive frame of a building, the cytoskeleton is constantly restructured, which allows for movement (1). The cytoskeleton is formed by three main structural units and associated proteins: microfilaments, microtubules and intermediate filaments. Intermediate filaments are divided into six types according to their molecular characteristics. Cytokeratins (CK) are type I and type II intermediate filaments (2, 3). Moll et al. (4) classified a total of 19 human epithelial keratins with variable molecular weights within the 40-70 kDa range, and subsequently an additional keratin was identified: CK20. They can be divided into low versus high molecular weight, and into acid or basic according to their isoelectric points (2).

CKs 14 and 19 are type I keratins: CK 19 is the smallest one and it is exceptional because, unlike other cytokeratins, it lacks the typical domain (no alpha helix) (5). CK14 is found in the keratinocytes of stratified squamous epithelium, both in the epidermis and the nonkeratinized mucosa (4), while CK19 is expressed in most simple epithelia, in various ductal epithelia, in intestinal epithelia, in the gastric foveolar epithelium, and in the mesothelium. Besides, it is present in most pseudostratified epithelia and urothelial cells, as well as in basal cells of nonkeratinized stratified squamous epithelium (4).
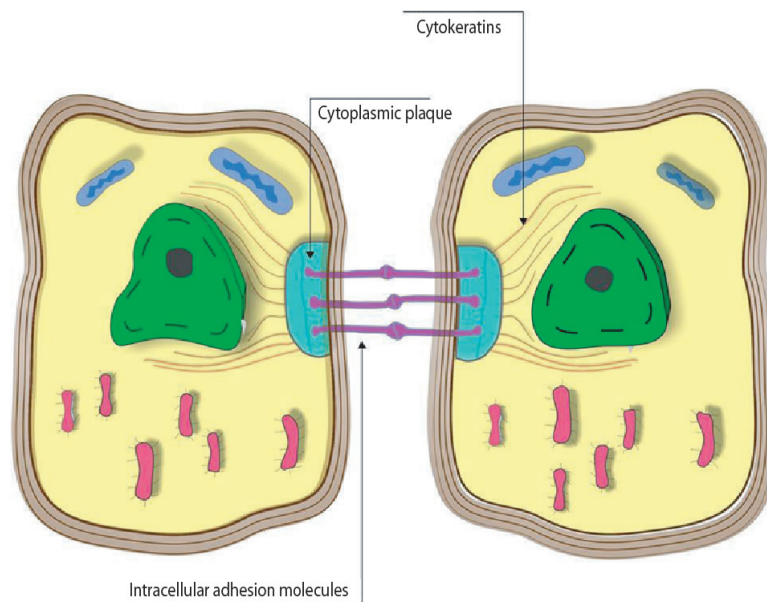

Fig. 1. Epithelial cells. Disposition of cytokeratins from the cytoplasmic plaque toward the nuclear periphery.

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Which are their functions?

Cytokeratins form a complex network which extends from the nucleus surface to the peripheral cell sector, where they are inserted into desmosomes and hemidesmosomes. (Figure 1). As they connect the nucleus surface with the plasma membrane, they provide a permanent link that can have important implications for cytoplasm organization, cell communication, and perhaps for the transportation of information inside and outside the nucleus (2, 4). Additionally, as they are inserted into desmosomes and hemidesmosomes, they contribute not only to the stability of epithelial cells, but to their union with the basal membrane and the underlying connective tissue (4, 6).

In recent years there has been agreement regarding the fact that keratins have two fundamental roles in epithelial cells:

a) structural support, without which physical trauma leads to loss of integrity, and

b) regulation of metabolic processes and their growth, proliferation, migration and apoptosis.

These two general roles involve regulated interactions with a diverse group of proteins (2, 7), which include signaling molecules such as 14-3-3 proteins, apoptosis-related proteins, kinases and phosphatases (8). Oriolo et al. (9) say that they can also have a role in epithelial polarity and membrane traffic.

Cytokeratins have also been linked to wound healing, as they provide a more pliable cytoskeleton to the cell, which favors the migration of keratinocytes for wound closure (10). As for CK14, mutations in the CK genes are responsible for epidermolysis bullosa simplex (11, 12), a hereditary disease, considered important for the physical stability of the epidermis (4). In turn, CKs 15 and 20 have been used as diagnosis and prognosis markers in various tumors of epithelial origin (13, 14).

Utility of cytokeratins as markers

Not all keratins are synthesized simultaneously by a cell, but rather different subsets of keratins are expressed during terminal differentiation in different stages of development, as well as in different epithelia. Therefore, all epithelia (simple and complex) can be classified according to cytokeratin expression. Simple or monostratified epithelia generally express keratins 7, 18, 19 and 20, while complex (stratified) epithelia express keratins 5, 6, 10, 14 and 15. When an epithelium undergoes malignant transformation, its keratin profile usually remains constant (2). Therefore, patterns of keratin expression allow us not only to identify a cell as epithelial, but also to determine the phases of epithelial differentiation and to characterize the tumor. This is why antibodies against several keratins are used routinely at immunohistochemistry labs to diagnose carcinoma, especially unclear metastases (4).

Another clinical application is the detection of protein fragments of CK8, CK18 and CK19 in the bloodstream of cancer patients. These fragments are increasingly used to monitor tumor burden and the progression of the disease in certain carcinomas such as lung cancer (15, 16). Besides, it has been observed that over 95% of lung carcinoma squamous cells are positive for CK14 (13, 17).

CK19 is one of the most frequently studied immunohistochemical markers in thyroid pathology, which could make it a useful diagnosis and prognosis tool, as it can be determined before the therapeutic procedure in cytologic findings (14).

Immunohistochemical staining for CK19 facilitates the differential diagnosis between papillary carcinoma, which presents strong and diffuse staining, and other thyroid cancers, which present weak and focal staining. It has also been suggested that it could be a

useful predictor of the progression of thyroid carcinoma (14).

Tsuruba et al. (18) showed that CK8 and CK14 can be useful to diagnose tumors in skin appendices. In general, the following tumors test negative for CK8 and positive for CK14: epidermis, sebaceous glands and hair follicles, while tumors derived from eccrine glands and apocrine sweat glands are CK8 positive and CK14 negative.

Squamous cells carcinoma, as well as malignant mesothelioma, show a strong expression of CK14, while adenocarcinomas show none or very little (2, 4, 19). Studies have suggested that the expression of certain keratins of simple epithelia (like CK19) in squamous cells carcinomas may indicate a poorly differentiated carcinoma (4). CK19 is detected in the epithelium near squamous cells carcinomas, which suggests that it could be used as a fundamental biological agent of the malignant progression (20). Clearly these findings can be applied in the case of oral cavity squamous cells, which shows the utility of these cytokeratins in the diagnosis and as a possible prognosis factor in diverse neoplasms that affect the maxillofacial region (21), as well as lesions of the oral mucosa considered potentially malignant (22, 23).

As for salivary glands tumors, they can be divided into two large categories: tumors derived from stratified epithelium (pleomorphic adenoma, myoepithelioma, basaloid squamous cells carcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma), and tumors that arise from simple epithelia (adenocarcinoma NOS, monomorphic adenocarcinoma and acinar cell carcinoma). The former express CK14 and CK19, while the latter do not (24, 25). CK14 is a myoepithelial cells marker, therefore, salivary glands tumors with myoepithelial cells are usually positive for CK14. These tumors include be-

nign or malignant myoepithelioma, adenoid cystic carcinoma and pleomorphic adenoma (13, 26, 27).

Cytokeratins and odontogenesis

Patterns of expression of cytokeratins in the odontogenic epithelium have been described in a very general way. Domingues et al. (28), in their immunohistochemical study, showed that epithelial cells of the tooth germ and in the remnants of the dental lamina are positive for CK14 and CK19 with slight changes in their expression pattern, depending on the phase of odontogenesis. For example, they state that at the inner epithelium of the enamel organ the expression of CK14 and CK19 varies in the follicle and bell stages (early bell stage according to the author). They observed a strong positive for CK14 while CK 19 had weak staining, which was the opposite at the late bell or follicle stage. CK19 has a strong positive, while the expression of CK14 decreases. Additionally, the most prevalent cytokeratin in the remnants of the dental lamina was CK14, which strongly stained all cells, while CK19 appeared only in some cells of the dental lamina, with a non-homogeneous pattern. CK14 was also observed in the stellate reticulum, which was stronger at the early bell phase. CK19 was also expressed but more weakly. The outer epithelium of the enamel organ was marked for CK14 and for CK19. Crivelini et al. (20), Ferreira Lopes et al. (29), Leon et al. (30), Kasper et al. (31), Heikinheimo et al. (32), and Gao et al. (33) also studied the expression of CK14 and CK19 in tooth germ, although in less detail.

They found CK14 and CK19 in the enamel organ (20, 29–33) and in the dental lamina (20, 30, 31).

Crivelini et al. and Leon et al. agree with the findings of Domingues et al. As for CK14, it is gradually replaced by CK19 in the inner

epithelium of the enamel organ: immunoexpression of CK19 is very positive in preameloblasts (32).

Given the changes in the expression of CK14 and CK19 in the inner epithelium of the enamel, some researchers have suggested that CK19 could be considered an effective marker of ameloblast differentiation (20, 28).

Odontogenic cysts and tumors

The presence of these cytokeratins in tooth development suggests that they participate in the embryonic development of the dental organ, which is why various authors have studied their expression in odontogenic cysts and tumors (20, 29, 30, 32–47). Patterns of expression of keratins allow us to identify a cell as epithelial and also to identify different stages during epithelial differentiation (4). Antibodies against these cytokeratins have been used to elucidate histogenesis and to characterize the tumor. Numerous biomedical studies have illustrated the utility of these two cytokeratins to identify odontogenic epithelium, and therefore they have been useful in the diagnosis of some neoplasms or cysts where an odontogenic origin is suspected. They have also been useful to determine the possible histogenesis of several cystic or tumoral lesions of the maxillofacial region that are known to be of odontogenic origin (20, 29, 30, 32–34, 37, 40–45, 47). An example of this are the studies conducted in ameloblastomas (20, 29, 34–36), where the expression of CK14 and CK19 was studied to elucidate its possible origin (20, 29). Other authors have studied these same cytokeratins to differentiate them from other lesions, for example Yoon et al., who studied the expression of CK14 and CK19 to differentiate it from ameloblastic carcinoma. They found that in both tumors the expression of both cytokeratins is strong and diffuse. Another interesting study is that of Pal et al. (35), who studied the expression of these same cytokeratins in central ameloblas-

toma and in peripheral ameloblastoma. They conclude that CK19 expression can be used as a tool to differentiate both neoplasms since in the cases of central ameloblastomas studied, CK19 is positive in all the cells, while in peripheral ameloblastoma, there are CK19 negative cells. Gao et al. (33) studied the expression of CK14 and CK19 in the odontogenic epithelium of normal dental follicles, as well as in the epithelium of dentigerous cysts and keratocystic odontogenic tumors, as they all derive from the odontogenic epithelium of the dental organ. These patterns were compared with cysts of different origins, like nasopalatine cysts and epidermoid cysts. The results obtained confirmed the prediction that development cysts from the odontogenic epithelium shared the expression of CK14 and CK19, but they were different from the cysts originated in non-odontogenic epithelium. Therefore, odontogenic epithelium and its derivates (cysts and tumors) show certain similarities in their patterns of expression of CK, but they differ from nasopalatine cysts for example, which derive from epithelial remnants of the nasopalatine duct, and from epidermoid cysts, which arise from the epithelium during embryonic development.

In Table 1 we summarize the studies which have focused on the expression of CK14 and/or CK19 in various odontogenic cysts and tumors.

Table 1.- Expression of CK14/CK19 in odontogenic cysts and tumors. 1989–2013 literature review.

ODONTOGENIC TUMORS AND CYSTS	AUTHOR	YEAR	CK14 expression	CK19 expression	Origin
Solid ameloblastoma	Crivelini et al. (20)	2003	CK14 positive	CK 19 positive	Remnants of dental lamina
	Ferreira Lopes et al. (29)	2005	CK14 positive in the cells of the periphery of tumoral nests	CK 19 positive, in central and peripheral cells	Remnants of dental lamina
	Ferreira Lopes et al. (29)	2005	CK14 positive in the cells of the periphery of tumoral nests	CK 19 positive, in central and peripheral cells	Remnants of dental lamina
	Yoon et al. (34)	2011	Strong positive for CK14	Positive for CK19	Remnants of dental lamina (enamel organ)
	Pal et al. (35)	2013	<u>Follicular:</u> Positive for CK14 in all basal cells and in most internal cells <u>Plexiform:</u> Positive for CK14 in all basal cells and in most internal cells <u>Microcystic:</u> Positive for CK14 in all basal cells and in most internal cells <u>Acanthomatous:</u> Positive for CK14 in all basal cells and weak positive in internal cells <u>Granular:</u> Negative for CK14	<u>Follicular:</u> Positive for CK19 in all cells <u>Plexiform:</u> Positive for CK19 in all cells <u>Microcystic:</u> Positive for CK19 in all cells <u>Acanthomatous:</u> Positive for CK19 in all cells <u>Granular:</u> Weak positive for CK19	----------------
	Fukumashi et al. (36)	2002	--------------------	<u>Follicular:</u> Positive for CK19 in all cells <u>Plexiform:</u> Positive for CK19 in all cells <u>Acanthomatous:</u> Positive for CK19 in all cells <u>Granular:</u> Positive for CK19 in basal cells and weak positive in suprabasal and internal cells.	----------------
Peripheral ameloblastoma	Kishino et al. (37)	2007	Positive for CK14	Positive for CK19	Remnants of odontogenic epithelium
	Pal et al. (35)	2013	---------------------	Positive for CK19, although some negative cells were found at internal and basal levels.	----------------

			CK14	CK19	Origin
Desmoplastic ameloblastoma	Pal et al. (35)	2013	----------------------	Positive for CK19, although some negative cells were found at internal and basal levels.	------------------
	Fukumashi et al. (36)	2002	---------------------	Positive for CK 19 in all internal and suprabasal cells	------------------
	Bologna-Molina et al. (38)	2010	Positive for CK14 in some suprabasal cells and in central cells	Negative for CK19	-------------------
Calcifying epithelial odontogenic tumor	Crivelini et al. (20)	2003	Positive for CK14 in all cells	Weak positive for CK19	Remnants of Hertwig's sheath
Adenomatoid odontogenic tumor	Crivelini et al. (20)	2003	Positive for CK14 in all tumoral epithelial cells	Negative for CK19.	Reduced enamel epithelium
	Leon et al. (30)	2005	Positive for CK14 in all cells Some negative cases for clear cells (cells in the center of nodes)	Positive for CK19 less intense than positive for CK14 Negative in fusiform cells (peripheral to the nodes)	Reduced enamel epithelium
	Ferreira Lopes et al. (29)	2005	Positive for CK14 positive in duct and plexiform cells	Positive for CK 19 in duct cells	Reduced enamel epithelium
Odontogenic myxoma	Martínez-Mata et al. (39)	2008	Positive for CK14	Partially positive for CK19	------------------
Ameloblastic fibroma	Crivelini et al. (20)	2003	Positive for CK14 in all the epithelium	Negative for CK19	Remnants of dental lamina
Ameloblastic fibrodentinoma	Bologna-Molina et al. (40)	2013	-----------------------	Strong positive for CK19	Odontogenic epithelium
Keratocystic odontogenic tumor	Gao et al. (33)	1989	Positive for CK14.	Positive for CK 19 (irregular staining in suprabasal cells and in some basal cells)	Remnants of dental lamina
	Dos Santos et al. (41)	2009	Positive for CK14 in all epithelial layers	Strong positive for CK19 (in suprabasal and intermediate cells)	Remnants of dental lamina
	Aragaki et al. (42)	2010	--------------------	Strong positive for CK19 (in basal and suprabasal cells)	From remnants of the dental lamina
Dentigerous cysts	Gao et al. (33)	1989	Positive for CK14	Strong positive for CK19	Reduced enamel epithelium
	Tsuji et al. (43)	2013	--------------------	Positive for CK 19 (in the basal layer of squamous epithelial cells)	Odontogenic epithelium
	Stoll et al. (44)	2005	--------------------	Positive for CK19	Odontogenic epithelium

Calcifying epithelial odontogenic cyst	Lukinmaa et al. (45)	1997	Strong positive for CK14	Strong positive for CK19 (cells of the basal layer of the epithelium)	Odontogenic epithelium
	Murakami et al. (46)	2003	---------------------	Positive for CK19 (in basal cells of oral mucosa).	------------------
	Fregnani et al. (47)	2003	Positive for CK14 (in basal cells of lining epithelium)	Positive for CK19 (in suprabasal cells of epithelium)	Odontogenic epithelium

In conclusion, various studies and recent research increasingly ascribe cytokeratins a role which goes well beyond the mere construction of the cytoskeleton. Several groups are currently studying the influence of their structural and regulatory functions in various diseases, and the molecular interactions of these proteins in various normal and pathological processes are becoming increasingly clear. These new findings highlight the importance of this family of intermediate filaments as useful biomarkers for the prognosis and diagnosis of various human tumors, including those in the oral maxillofacial region.

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