10.5005/jp-journals-10024-1573

REVIEW ARTICLE

The Ambiguous Salivary Myoepithelial Cells

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ABSTRACT

Salivary gland neoplasms present with a diverse histological pattern which is mainly because of the presence of specialized myoepithelial cells (MECs). These are contractile epithelial cells with smooth muscle like properties. They have been also noticed in mammary glands, lacrimal glands, prostate gland, and the sweat glands and have varied functions. MECs play an important role in the histogenesis of many salivary gland tumors. Knowledge of MECs leads to a better understanding of the histological diversity of salivary gland neoplasms. This article reviews the physiology, histology, identification and role of these cells in salivary gland pathology.

Keywords: Myoepithelial cells, Salivary gland neoplasms, Calponin, Basket cells.

How to cite this article: Rao RS, Patil S, Amrutha N, Sanketh DS, Agarwal A. The Ambiguous Salivary Myoepithelial Cells. J Contemp Dent Pract 2014;15(4):523-528.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

MECs are cells that are known for its hybrid epithelial and mesenchymal phenotype (both structural and functional). MECs are located in the salivary glands, mammary glands, lacrimal glands, prostate gland and in the sweat glands. In the salivary glands, these cells lie between the basement membrane and basal plasma membrane of the acinar secretory cells and intercalated duct cells. There is usually one myoepithelial cell per secretory end piece, but two or three may sometimes be seen[1] (Fig. 1).

Krause (1865) first described MECs cells in the parotid gland of the cat and their earliest description in human salivary glands is attributed to Zimmerman (1898).[2] The term 'myoepithelial cells' was coined by Kolossow (1898).[3,4]

MECs are also called basket cells as their shape appears like a basket cradling the secretory cells. Other synonyms used for these enigmatic cells are octopus sitting on a rock (owing to its location) and cinderella cells (used for MECs of the mammary glands).[5,6]

The term myoepithelial cells is used because these cells have an epithelial origin but a muscle like contractile function.[7] Characteristically, presence of cytoplasmic filaments on the basal side consisting of myofilaments like actin, tropomyosin and myosin are seen which are arranged in a pattern similar to that of smooth muscle.[8]

These cells have a diverse morphology, varied functions and an important role in the histogenesis of many salivary gland neoplasms, therefore this article aims to review its participation and role in salivary gland physiology and pathology.

FUNCTIONS

The functions of myoepithelial cells are:[3,4,7,9,10] (Table 1).

DEVELOPMENT

The MECs development begins around the 18th day *in utero*. The fetal oral epithelium produces committed pluripotent stem cells which give rise to the ductal progenitor cells in the cellular cord and the acinar progenitor cells in the terminal bud. Later acinar progenitor differentiates into luminal cells (acinar cells and intercalated duct cells) and MECs, whereas the ductal progenitor differentiates into ductal luminal and basal cells[9,11] (Fig. 2).

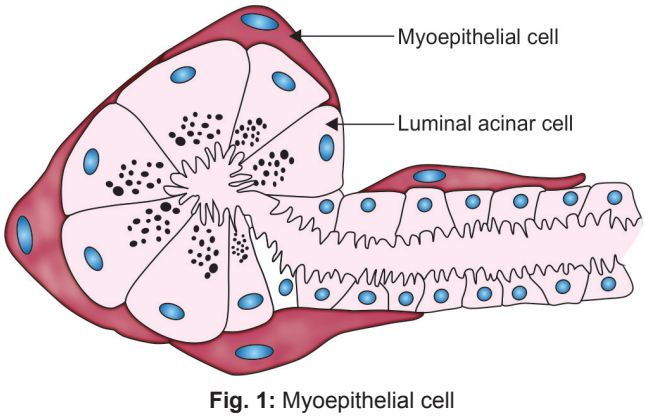

Fig. 1: Myoepithelial cell

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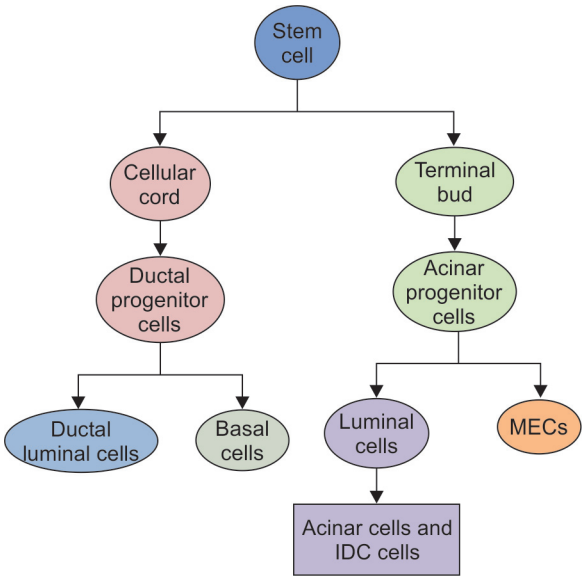

Fig. 2: Development of myoepithelial cells

ULTRASTRUCTURE

MECs associated with the secretory units have been described as 'an octopus sitting on a rock' or a basket cradling the secretory unit. Each cell consists of a central body from which 4 to 8 cytoplasmic processes radiate, which further branch out and embrace the acinar cells.[1,12,13]

Ultrastructurally MECs can be divided into a filamentous and a nonfilamentous compartment:

Filamentous Compartment

- A flattened nucleus and few cytoplasmic organelles like golgi complexes, liposome bodies and mitochondria mainly located in the perinuclear region.

Nonfilamentous Compartment

- Bulk of cytoplasm contains numerous contractile actin and myosin microfilaments 4 to 8 μm in diameter and cytokeratin intermediate filaments 8 to 10 nm in diameter. (Microfilament arrangement is similar to that seen in smooth muscle cells).
- Presence of cytokeratin intermediate filaments confirms the epithelial origin of MECs and distinguishes them from smooth muscle cells which contain desmin.
- Numerous caveolae are present on the plasma membrane mainly on the basal side.
- MECs are attached to luminal cells and to each other by desmosomes and gap junctions and to basal lamina by hemidesmosomes.[3,4,9,11]
- Many authors like Tandler (1965), Cutler and Chaudhury (1973) and Garatt and Emmelin (1979) suggested the presence of a cilum on salivary MECs which may have a chemoreceptor or a mechanoreceptor role.[1]
- Differences between the MECs present around secretory end pieces and intercalated ducts have been enumerated below. MECs are said to be absent around striated ducts[1,12] (Table 2).

Table 1: Functions of myoepithelial cells

Contractile function	Contractions help to expel the secretions from the acini. Provides support for the end piece, preventing an over distension as the secretory products accumulate within the cytoplasm. It contracts and widens the diameter of the intercalated ducts, and maintains their patency. Supports the underlying parenchyma and reduces the back permeation of liquid.
Formation and maintenance of basement membrane	Through secretion of laminin and elastin.
Inhibit tissue invasion and metastasis	Tumor suppressor activity via secretion of proteinase inhibitors and antiangiogenesis factors.

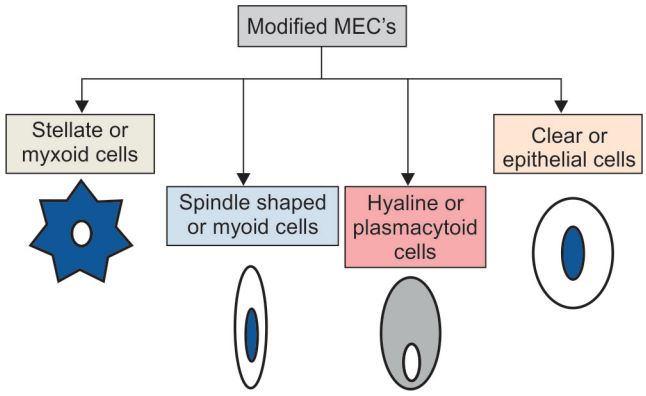

Fig. 3: Modified myoepithelial cells

MODIFIED MEC's

Myoepithelial like cells or the so called 'modified' MECs are derived from the neoplastic myoepithelial cell as a result of metaplasia, dedifferentiation and trans differentiation processes.[12]

These can be seen under light microscope in various combinations in different salivary gland tumors. They are depicted in Figure 3.

Table 2: Differences in myoepithelial cells around acinar and ducts

Acinar MEC	*Ductal MEC*
1. Stellate shape or spiderlike	1. Spindle shaped
2. Numerous long branching processes extending from the cell body with numerous microfilaments	2. Few short processes with scarcity or absence of fibrils
3. End pieces myoepithelial processes crosses but does not extend onto ducts	3. Myoepithelial processes seldom branch and overlap with those of the end pieces

MECs in disease/neoplastic MECs have a varied morphology. They are:

i. *Stellate/myxoid*: Star shaped cells with centrally located nucleus.
ii. *Spindle/myoid*: These cells are elongated, fusiform with pale cytoplasm.
iii. *Plamacytoid/hyaline*: These cells have bright eosinophilic cytoplasm with eccentric nuclei.
iv. *Clear/epithelial cell type*: These cells contain clear cytoplasm due to glycogen.

SALIVARY GLAND NEOPLASMS INVOLVING MECS

A working classification based on the participation of myoepithelial cells is enlisted below[9,14,15] (Table 3).

ROLE OF MECs IN SALIVARY GLAND DISEASES[14,16-21]

Histogenetic Concepts

Semipluripotential Bicellular Reserve Cell Hypothesis

Eversole postulated that specific reserve/basal cells of the excretory and intercalated ducts are responsible for replacement of all the types of cells in a normal salivary gland and hence are the source of neoplastic transformation. But many findings have negated this theory.

Multicellular Histogenetic Concept

It was seen that mitotic figures were more frequently seen in luminal cells than in basal cells. Luminal epithelial cells with mitotic figures are present in intercalated, excretory and even the striated ducts. This suggests that any of the cells found in the normal salivary gland could serve as a precursor for neoplasia and hence, this concept is widely accepted now.

To understand the histologic pattern of salivary gland tumors, it is essential to appreciate the:

i. Role of the tumor cell organisation.
ii. Types of cellular differentiation.
iii. Materials synthesized within the tumor.

MYOEPITHELIOMA

Exclusively composed of modified MECs with total absence of ductal component, presence of a minor epithelial component (5-10%) may be seen. Diagnosis is made in the absence of chondroid interstitial deposits and epithelial differentiation (usually in the form of ducts).It represents one extreme end of the histomorphologic spectrum of mixed tumor but has been identified separately owing to their monomorphic appearance.

ME Component

Neoplastic MECs can be spindle, plasmacytoid hyaline, epitheloid or clear. Principally three types of myoepithelioma are recognized. They are composed of:

i. Plasmacytoid or hyaline cells are — similar to those seen in pleomorphic adenoma which form islands, sheets or are present as aggregates in a myxoid stroma devoid of chondroid differentiation.
ii. Epithelial cells — are large polygonal cells with eosinophillic cytoplasm and centrally located bland nuclei in a reticular, trabecular or solid growth pattern.
iii. Fibroblastic or myoid cells — the spindle cell pattern is most common and consists of proliferation of elongated cells with central vesicular nuclei and eosinophillic cytoplasm in sheets/fascicles.

Table 3: Classification of salivary gland neoplasms based on myoepithelial cells participation

Neoplasms	*Benign*	*Malignant*
Tumors with major myoepithelial participation	Myoepithelioma	Myoepithelial carcinoma
Tumors with epithelial myoepithelial participation (Biphasic)	1. Basal cell adenoma 2. Pleomorphic adenoma 3. Warthin's tumour	1. Epithelial myoepithelial carcinoma 2. Adenoid cystic carcinoma 3. Basal cell adenocarcinoma 4. Polymorphous low grade adenocarcinoma 5. Ca ex pleomorphic adenoma 6. Metastasising pleomorphic adenoma
Tumors with minor myoepithelial participation		1. Mucoepidermoid carcinoma 2. Sebaceous adenocarcinoma 3. Salivary duct carcinoma
Tumors devoid of myoepithelial participation	1. Canalicular adenoma 2. Ductal papilloma 3. Cystadenoma 4. Oncocytoma	1. Acinic cell carcinoma 2. Oncocytic carcinoma 3. Adenocarcinoma

iv. Clear cells—rich in glycogen are usually present only focally, but can sometimes be prominent.

PLEOMORPHIC ADENOMA

Diverse histologic patterns and cytological features can be appreciated in pleomorphic adenoma due to the multiplicity of differentiation pathways. Characterized by differentiation of both luminal and nonluminal cells. Areas composed principally, of ducts with associated MECs, of only modified MECs or a combination of the two cell types is seen.

ME Component

Neoplastic ME component can assume a variety of cell forms such as spindle, plasmacytoid, stellate, hydropic clear cell and epitheloid. They can form sheets, trabeculae and even cribriform structures.

Plasmacytoid hyaline cells are the most distinctive form of MEC. Their occurrence is restricted to pleomorphic adenoma and myoepithelioma, therefore their identification is of great importance.

Stellate MECs occur singly, or form anastomosing strands in a myxoid matrix. Sometimes, MECs form squamous nests suggesting differentiation toward a squamous lineage.

Stroma

There is some evidence that the stroma is composed of the acidic mucosubstances produced by the modified MEC. Basal lamina, elastic and collagen fibers, and glycosaminoglycans are the main secretory products. Production of these substances and gradual separation of the extracellular matrix with eventual development of chondroid, myxoid, chondromyxoid, hyaline and sometimes osseous and adipose areas takes place.

ADENOID CYSTIC CARCINOMA (ACC)

ACC is an invasive neoplasm composed of predominantly two cell populations: ductal cells and MECs. It is characterized by cribriform, solid and tubular patterns of growth. Diagnosis requires the identification of small duct like structures within the bulk of modified MECs that form the basal lamina lined 'pseudocysts' in the cribriform structures. Similar morphogenetic mechanisms produce the histologic variants seen in ACC.

ME Component

Neoplastic basaloid MECs constitute the major cell population. They possess round/angulated nuclei with scanty cytoplasm and indistinct cell borders. The MECs are found in the 'pseudocyst' lining cells of the cribriform pattern, nonluminal cells of the tubular pattern, and the component tumor cells of the cribriform and solid patterns.

Stroma

Stroma of the tumor is usually fibrous, at times may be hyalinized. But the spaces encountered in the cribriform pattern contain eosinophillic hyaline material which has been proven to be glycosaminoglycans and duplicated basal lamina.

BASAL CELL ADENOMA

This tumor is composed of basaloid cells sharply delineated from the stroma by basement membrane like material. Chondromyxoid stroma is characteristically absent in this tumor.

ME Component

The presence and contribution of MECs is controversial. Dardick postulates that the tumor represents a hybrid of basal cell adenoma and myoepithelioma/cellular pleomorphic adenoma.

Stroma

Another evidence of myoepithelial participation in basal cell adenoma is presence of a hyalinized matrix.

EPITHELIAL MYOEPITHELIAL CARCINOMA

It is a biphasic malignant tumor composed of ductal structures, lined by a single layer of ductal cells which are surrounded by a single or multiple layers of clear myoepithelial cells.

ME Component

Generally, the clear myoepithelial cell component predominates and these appear polygonal and large with abundant water clear cytoplasm. The cytoplasmic clearing is due to accumulation of glycogen. Neoplasms with a predominant clear cell myoepithelial component can be mistaken for a clear cell adenoma.

Stroma

The tumor's growth pattern varies from solid lobules separated by bands of hyalinized, vascular, fibrous connective tissue to irregular papillary cystic arrangements with tumor cells that partially or completely fill the cystic spaces.

POLYMORPHOUS LOW GRADE ADENOCARCINOMA

ME Component

Origin is proposed from the intercalated duct showing derivation from both ductal and myoepithelial cells. Focal

Table 4: Identification of myoepithelial cells

Special stains		• Phosphotungstic acid hematoxylin (PTAH) • Heidenhains irons hematoxylin (IH) • Levanol fast cyanine (Coomassie blue)	
Enzyme histochemistry		• Adenosine triphosphates	
Immunohistochemistry			
	Marker	*Positivity*	*Use*
1. Microfilament proteins	A-SMA MSA (muscle specific actin)	MECs	High specificity, very useful
	SMMHC (smooth muscle myosin heavy chain)	MECs	Poor sensitivity
	H-caldesmon	MECs	Poor sensitivity
	Basic calponin	MECs	High specificity, very useful
2. Intermediate filament proteins	K14, K5, K17	MECs and basal cells	
3. Other proteins	S-100	MECs and ductal cells	Low sensitivity
	Vimentin	MECs and ductal cells	Low specificity
	α_1 β_1 Integrin	MECs (variable)	
	P63	MECs and basal cells	
	GFAP	MECs (variable)	Low specificity

staining with smooth muscle markers has been detected in this lesion. MECs are absent or present very focally when observed through a light microscope but the electron microscope reveals that a minor population of abluminal cells are present.

Stroma

The tumor cells are surrounded by a hyalinized eosinophillic stroma that occasionally displays a myxoid change. A slate gray blue stroma is said to be characteristic.

MUCOEPIDERMOID CARCINOMA

ME Component

Initially, this tumor had been thought to be devoid of MECs until recently, when an electron microscopic study revealed presence of tumor cells with numerous interlocking microvillous processes and basal, blunt cytoplasmic processes projecting into the stroma. MECs are found focally or forming sheets corresponding to the intermediate cells.

NON-NEOPLASTIC CONDITIONS

Myoepithelial participation is also seen in non-neoplastic lesions of the salivary glands like chronic recurrent sialadenitis, lymphoepithelial lesion, Sjogren's syndrome.

ME Component

These are all characterized by a lymphoreticular cell proliferation and atrophy of the parenchyma and ductal changes forming 'epimyoepithelial islands'. Metaplastic proliferation of ductal epithelium accompanied by MECs forms these islands.[14,16-21]

Table 5: Immunchistochemical markers for salivary gland cells

Markers	*Luminal cells*		*Abluminal cells*	
	Acinar	*Ductal*	*MEC*	*Basal*
AE1/AE3	+	+	+	+
EMA	+	+	-	-
CEA	+	+	-	-
α amylase	+	-	-	-
CK14	-	-	+	+
p63	-	-	+	+
SMA	-	-	+	-
MSA	-	-	+	-
Calponin	-	-	+	-
Podoplanin	-	-	+	-
Vimentin	-	-	+	-
S-100	Variable	Variable	Variable	Variable
GFAP			Variable	

IDENTIFICATION OF MECs

Reliable identification of MECs, both normal and neoplastic can be achieved by a plethora of methods which have been enlisted below[9,15,19] (Tables 4 and 5).

CONCLUSION

Identification of neoplastic MECs leads to understanding the cellular composition of a tumor that is necessary to:

- Predict the cell of origin and the development of the histomorphology
- Predict the biologic behavior of a tumor. (Neoplasms with integral MEC participation are low grade with low ability to metastasize).

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