Review Article

Pathophysiology of myoepithelial cells in salivary glands

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Abstract

Myoepithelial cells (MECs) are considered to be a key participant in most salivary gland diseases, particularly tumors. MECs structurally resemble both epithelial cells and smooth muscles. Diagnostic dilemmas caused are due to inadequacy of characterizing the wide spectrum of morphologic and immunologic features which are different for both normal and neoplastic MECs. This article discusses the development, functions and structure of both normal and neoplastic MECs, their staining properties and differences in the morphologic and immunophenotypic properties of the MEC in detail. It also describes the role of MEC in pathogenesis and morphogenesis of various nonneoplastic and neoplastic salivary gland lesions and thereby are responsible for the myriad histopathology of salivary gland tumors.

Key Words: Myoepithelial cell, neoplasm, salivary gland tumor

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Received: 23.04.2015, **Accepted:** 17.08.2016

INTRODUCTION

In salivary glands and other exocrine glands, there are star-shaped cells lying between the basal lamina and the acinar and ductal cells. These cells structurally resemble epithelial cells and smooth muscles and, thus, are referred to as myoepithelial cells (MECs). Because of their shape and interwoven processes, they were commonly referred to as "star-shaped cells" or "basket cells." Tamarin described these cells as being "like an octopus sitting on a rock" [Figure 1].[1,2]

HISTORICAL INTRODUCTION

A brief history about the various terminologies used for these cells is shown in Table 1.[3,4]

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Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.190952

ORIGIN OF SALIVARY GLAND MYOEPITHELIAL CELLS

The salivary duct system is entirely epithelial in origin. The stem cells in the primordium differentiate into various components of the ducto-acinar unit including the secretory end pieces [Figure 2].[5]

DEVELOPMENT OF SALIVARY GLAND MYOEPITHELIAL CELLS

The various stages in the development of MECs are given in Table 2.[6]

DISTRIBUTION

MECs are located beneath the basement membrane of the terminal portion of most exocrine glands including

How to cite this article: Shah AA, Mulla AF, Mayank M. Pathophysiology of myoepithelial cells in salivary glands. J Oral Maxillofac Pathol 2016;20:480-90.

Table 1: History of myoepithelial cells

Author	Contribution
Krause (1865)	First discovered "star-shaped cells" in cat parotid gland
Heidenhain and Boll	Termed them as "basket cells"
Boll (1860)	Suggested they had a supporting role in the reticular tissue. The French investigators termed "cellules de boll"
Kolossow (1898)	Termed them as "muscular epithelial cells"
Zimmerman (1898)	Identified MECs in human salivary glands and on a suggestion by Renaut, he renamed these cells as "MECs"

MECs: Myoepithelial cells

salivary, lacrimal, mammary and sweat glands. They have variable distribution among the glands and species and also occasionally within the same gland during the development.[2]

In salivary glands, they are typically arranged to form arcs around the acini and orient along the long axes of ducts. In the major salivary glands, MECs are seen in relation to acini, intercalated ducts and striated ducts. Whereas, in the minor salivary glands, MECs invest the acini with processes continuing onto intercalated ducts. The excretory ducts and rather rudimentary striated ducts are devoid of MECs [Figure 3].

FUNCTIONS OF MYOEPITHELIAL CELLS

They serve diverse functions as follows.

Epithelial cell differentiation

During embryonic development, MECs are involved in the branching morphogenesis of the developing salivary glands and the promotion of epithelial cell differentiation by secreting growth factors and cytokines (basic fibroblast growth factor, transforming growth factor α and interleukin-6).[7]

Contractile function

Contraction of MEC facilitates expulsion of secretion by rupturing "ripe" mucous cells, reducing luminal volume and preventing distention of acini.

Contraction of elongated MECs along the intercalated ducts helps overcome peripheral resistance.[8-13]

Sensory

Myoepithelial cilia projecting into the invaginations in adjacent secretory cells may act as chemoreceptors.[14]

Maintenance of gland patency

Extension of MEC processes onto proximal regions of allied acini facilitates rigidity and patency in glands which may become distorted by masticatory movements.[10]

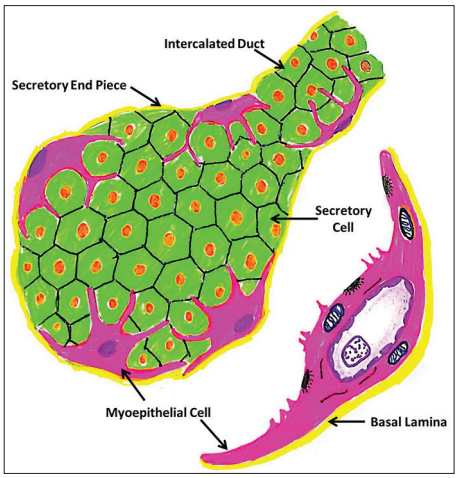


Figure 1: Diagrammatic representation of Myoepithelial Cells (Image modified from: Antonio Nanci: TenCate's Oral Histology: Development, Structure, and Function 8th edition. Elsevier Mosby

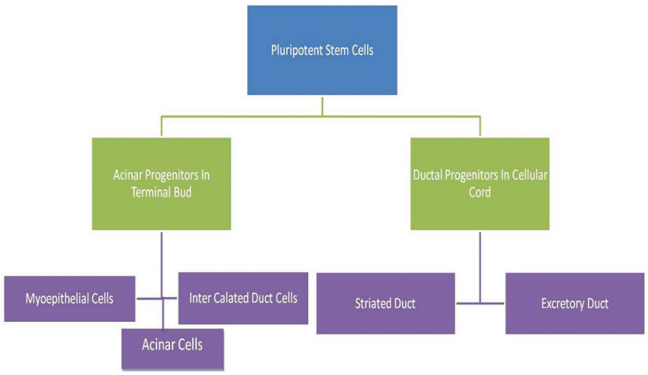


Figure 2: Origin of ducto-acinar components of salivary glands from pluripotent stem cells

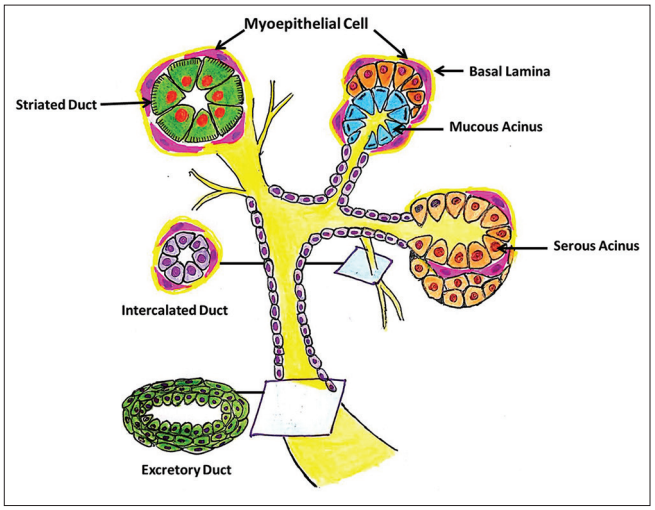


Figure 3: Diagrammatic representation of the distribution of MECs along the ducto-acinar units of salivary gland

Transportation of metabolites

The role of MECs in this is questionable. However, the presence of pinocytic vesicles, a positive staining for iron-binding

protein ferritin and high levels of alkaline phosphatase and magnesium-dependent ATPase activity suggests that MECs are involved in transportation of metabolites in the secretory process.[9,14-21]

Formation and maintenance of basement membrane

MECs play an important role by producing fibronectin, laminin and elastin, which are major components of basement membrane and extracellular matrix (ECM).

Interestingly, with neoplastic transformation, MECs usually augment and modify this matrix-synthesizing ability resulting in production of large amounts of both basement membrane and nonbasement membrane elements, the latter often predominating. The most dominant component of the nonbasement membrane matrix is chondroitin sulfate proteoglycan. The other forms of matrix produced by the MECs is eosinophilic hyalinized material, which represents the basement membrane-related proteins (type IV collagen and laminin) and interstitial matrix proteins (fibronectin, type I and II collagens).[18,21]

Tumor suppression

There is evidence that MECs also produce a number of proteins that have tumor-suppressor activity, such as proteinase inhibitors and anti-angiogenesis factors, which act as barriers against invasive epithelial neoplasms.

The MECs exert a paracrine anti-invasive effect by promoting epithelial differentiation, synthesis of basement membrane, secreting proteinase inhibitors and inhibiting angiogenesis.[22,23] The other properties of MEC signifying a tumor-suppressor role include secretion of high levels of maspin (an inhibitor of tumor growth and invasion) and tissue inhibitor of metalloproteinase-1, protease nexin II and α1-antitrypsin.[7,22,23]

STRUCTURE OF MYOEPITHELIAL CELLS

MECs appear considerably similar in structure, irrespective of the organ or species. MECs on acini have 4–8 primary cytoplasmic processes each showing 2 or more secondary branching processes. SEM also revealed that MEC processes ramify into numerous secondary and tertiary divisions. There can be up to thirty terminal processes extending from each MEC. The average number of processes extending from MECs is more in submandibular gland as compared to sublingual gland. It is also noted that the thicker MEC processes occur on the glands with more viscous secretions [Figure 4].[2,24]

The outer surface of MECs contains abundant caveolar invaginations in areas where nerve fibers abut. The smooth

Figure 4: Structure of myoepithelial cells showing cell body (arrow) and numerous cytoplasmic processes surrounding the acini (Coutesy: Antonio Nanci: TenCate's Oral Histology: Development, Structure, and Function 8th edition. Elsevier Mosby)

Table 2: Stages in development of myoepithelial cell

Phase of development	Stage in fetal life (weeks)	Features
Early development stage	10–18	Initiation Primitive MECs appear in the salivary gland epithelium before the cytological differentiation of acinar and ductal luminal cells
Early intermediate developmental stage	19–24	Structural changes MECs express actin filaments before the maturation of the acinar and ductal luminal cells takes place With maturation of the acinar cells, the MECs undergo cytoplasmic extension and take place in the basal portions of the acini and intercalated duct (Caselitz *et al*., 1981; Lee *et al*., 1991)
Late intermediate developmental stage	25–32	Maturation Cells get further flattened and dendritic at the basal portions of the acinar and intercalated duct structures Dendritic MECs mature at 25-26th week and become more conspicuous Increase in number during this stage and mature earlier to push the secretary material out of the acini toward the excretory ducts against the amniotic fluid pressure (Lee *et al*., 1991; Chi *et al*., 1996)
Late developmental stage	33–40	Proliferation MECs increase in number and develops contractile properties Cells which first developed in the acinar and intercalated ductal areas move toward the excretory ducts through the basal portions of the duct (Lee *et al*., 1991; Chi *et al*., 1996)

MECs: Myoepithelial cells

visceral surface is attached to secretory cells by desmosomes and may show isolated cilia invaginating the basal cytoplasmic membrane and protruding deep into the cytoplasm of the secretory epithelial cells.[25]

The MECs and their processes were filled with parallel streams of myofilaments which displayed focal densities. The myofilaments formed attachment plaques on the inner face of the plasmalemma. The cytoplasm contained ribosomes, polyribosomes, pinocytotic vesicles, vacuoles and lysosomes but contained few mitochondria and little rough endoplasmic reticulum. The nucleus is usually elongated, dense and irregular.[26]

The acinar MECs lie entirely on the epithelial side of the basal lamina. The intervening spaces between the MECs and the acinar cells display interdigitations and infoldings of the lateral plasma membrane. On the intercalated ducts, they are located between the basal lamina and ductal epithelium. Squamous metaplasia of MECs in this region is not uncommon and is characterized by the presence of numerous small and large tufts of cytoplasmic tonofilaments. MECs are also seen in association with the intralobular striated ducts and lie between the basal lamina and the ductal cells. Here, the MECs may be spindle-shaped, stellate, with their long axes are oriented parallel to the basal lamina. Occasionally, they may be oriented vertically, extending between the ductal cells or on top of another. Irrespective of their orientation, the MECs displayed similar ultrastructural features.[26]

Comparison of myoepithelial cells with smooth muscle cells

MECs share many features with smooth muscle cells. These include parallel arrays of filaments which are gathered in "dense bodies" and are anchored to the basal plasmalemma in attachment plaques; fusiform nuclei parallel to the long axis of the muscle cell or its longest processes; numerous caveolae, mostly in the basal plasmalemma; occasional collections of glycogen particles; sparse rough endoplasmic reticulum and Golgi zones and a basal lamina.[2]

MEC can be distinguished from smooth muscle cells in being attached to other parenchymal (acinar and ductal) cells and to each other by desmosomes and gap junctions and to the basal lamina by hemidesmosomes. In addition, smooth muscle cells are spindle shaped and bipolar while MECs have multiple processes[2,27,28] [Figure 5a and b].

NEOPLASTIC MYOEPITHELIAL CELLS

Basal and/or MECs form a continuum along the acini and ducts in the normal salivary gland. In salivary gland tumors largely composed of neoplastic basal and/or MECs, this relationship may persist. However, in some tumors, hybrid tumor cell forms are present along with typical basal and/or MECs or both.[29]

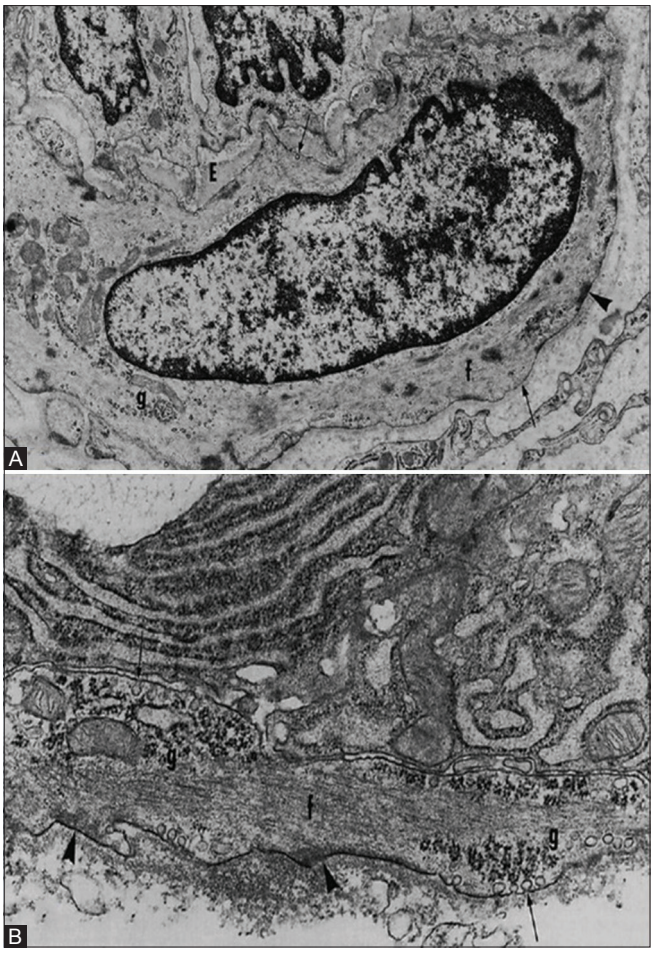


Figure 5: Comparison between myoepithelial cells and smooth muscle cells. (A) Smooth Muscle cell (B) Myoepithelial cell. There are groups of filaments (f); dense bodies; attachment plaques (arrowheads); caveolae (arrows) in the plasmalemma, that are more numerous basally; basal laminae; and focal collections of glycogen particles (g) (Redman R.S. Myoepithelium of Salivary Glands. Microscopy research and technique 2725-45 [1994])

Morphologic spectrum of neoplastic myoepithelial cell

Histologic diversity is the hallmark of neoplastic MECs. These cells have the potential to undergo divergent differentiation giving rise to different morphological cell types. The complex morphological patterns of neoplastic MEC results from a complex morphologic interplay of 3 characteristics:[30-33]

- Cytological differentiation
- Extracellular matrix production
- Architectural patterns.

Cytological differentiation

MECs potentially differentiate into various morphological cell types [Table 3]. Most tumors with MEC differentiation show more than one cell type.[7,34-36]

Extracellular matrix production

In the normal state, myoepithelium contributes to the synthesis of basement membrane components and ECM. This matrix-synthesizing ability is modified and augmented with their neoplastic transformation leading to production of abundance of both basement membrane and non-basement membrane elements.[22,23]

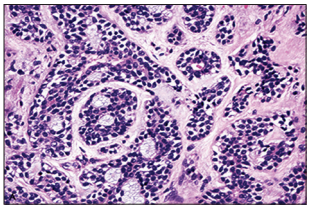
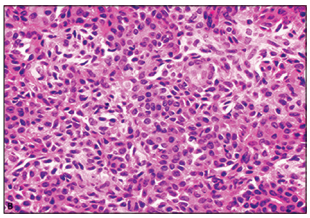
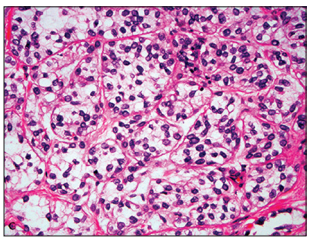
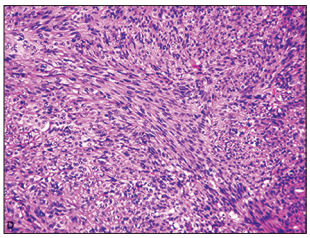
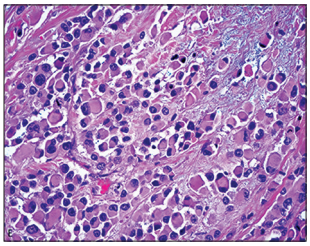
The most dominant component of the nonbasement matrix is chondroitin sulfate proteoglycan, which histologically appears as the bluish-gray myxochondroid material and is alcian blue positive. The other form of matrix produced by neoplastic myoepithelium is the eosinophilic hyalinized material, which represents the basement membrane-related (type IV collagen and laminin) and interstitial matrix (fibronectin and type I and type II collagens) components.[22]

Determining the true nature of ECM particularly the myxoid material is important in salivary gland tumor identification since it forms a component in various salivary gland tumors (SGTs) including pleomorphic adenoma, carcinoma ex pleomorphic adenoma and myoepithelioma.[22]

Architectural patterns

These cells can undergo metaplastic changes such as chondroid, squamous and oncocytic metaplasia. Dardick described various architectural differentiation patterns of MEC [Table 4].[7,29]

Table 3: Various cell types of myoepithelial cells due to cytological differentiation

Cell type	Description	Diagramatic representation
Angulate/ basaloid	Small hyperchromatic nuclei with faint eosinophilic cytoplasm	
Epitheloid	Polygonal with vesicular nuclei and ample cytoplasm	
Clear	Cells contain clear cytoplasm due to glycogen	
Spindle	Cells are elongated, fusiform with pale cytoplasm	
Plasmacytoid (hyaline)	Cells have bright eosinophilic cytoplasm with eccentric nuclei	

Courtesy: Savera AT, Zarbo RJ. Defining the role of myoepithelium in salivary gland neoplasia. Adv Anat Pathol 2004;11:69-85 and Dardick I. Color Atlas/Text of Salivary of Salivary Gland Tumor Pathology. 1st ed. NewYork: Igaku-Shoin Medical Publishers, Inc;. 1996

IDENTIFICATION OF MYOEPITHELIAL CELLS

Staining

Hematoxylin and eosin staining

In their normal environment, they are eosinophilic, birefringent structures which lie deep to the basement membranes of the secretory acini and smaller ducts and may appear fusiform or spider-like, depending on the plane of section. They stain intensely with phosphotungstic acid hematoxylin and iron hematoxylin [Figure 6].[24]

Special stains

A special staining procedure, the tannic acid-phosphomolybdic acid amido black technique of Puchtler and Leblond, has been found to be particularly suitable for staining myofibrils, thus demonstrating MECs.[37-39]

Enzyme histochemistry

ATPase was found to be the enzyme marker of MEC in human glands. However, although ATPase histochemistry can be helpful in identifying neoplastic MECs, some MECs in normal glands

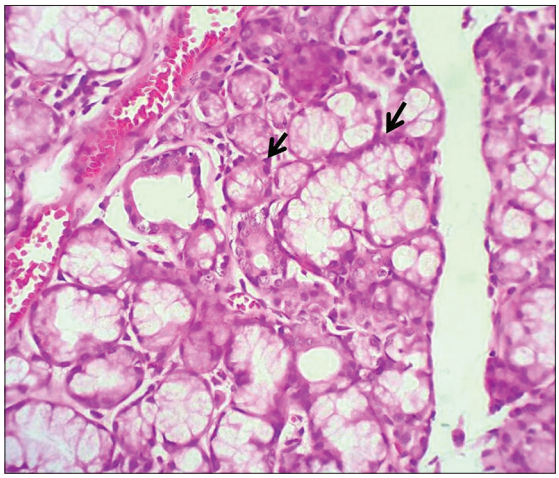
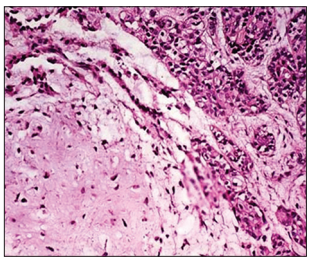
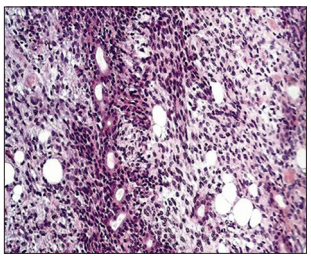
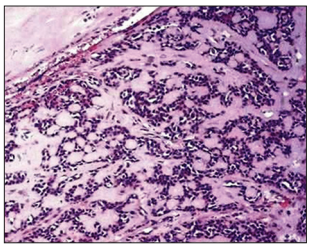
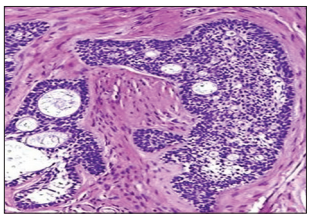
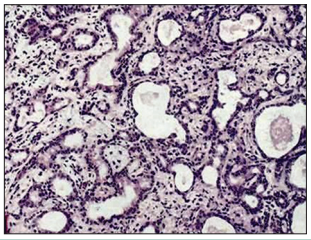


Figure 6: Demonstration of myoepithelial cells (H&E stain, ×400)

Table 4: Various architectural patterns of myoepithelial cell

Architectural patterns	Description	Diagramatic representation
Myxoid pattern	Tumor cells are loosely and randomly distributed due to production of abundant chondromyxoid matrix commonly seen in pleomorphic adenoma	
Solid pattern (nonmyxoid)	Cells in nests, sheets are seen with intervening hyalinized matrix generally seen in basal call adenoma	
Reticular pattern	Anastomozing pattern predominantly of epitheloid-MECs intervened by extracellular material commonly seen in canalicular adenoma	
Microcystic/pseudocystic pattern	Variable sized and loose cystic spaces formed by accumulating myxoid matrix within nests of tumor cells	
Cribriform/pseudoglandular pattern	Clusters of epitheloid cell form cribriform structures and pseudolumen due to their myxoid matrix production commonly associated with adenoid cystic carcinoma	

MECs: Myoepithelial cells. (Courtesy: Dardick I. Color Atlas/Text of Salivary of Salivary Gland Tumor Pathology. 1st ed. NewYork: Igaku-Shoin Medical Publishers, Inc;. 1996)

lack activity of this enzyme and persistence of enzyme activity in routinely processed specimens is too spotty to be reliable. A similar problem was encountered on examination of glycogen phosphorylase activity as a marker for neoplastic MEC.[40-45]

Immunocytochemistry

MECs can be best observed by immunocytochemistry. There are three types of immunocytochemical markers of MECs in salivary glands [Table 5].[46]

Due to the morphologic diversity of these cells, the immunohistochemical profile of neoplastic MECs has also been a perplexing issue. The reason for this is probably two-fold and interrelated as follows: First, immunophenotypic modifications are associated with neoplastic transformation which leads to variability/loss of immunoreactivity of some of the markers invariably present in normal myoepithelium (CK14, muscle markers [Figure 7]); second, there is expression of certain markers by neoplastic myoepithelium that are usually absent in nonneoplastic counterpart (S100 protein, vimentin and glial fibrillary acidic protein).[47,48]

The various markers seen during the development of salivary glands are shown in Table 6, and the various

markers used for demonstrating neoplastic MECs are given in Table 7.[46-57]

Electron microscopy

Transmission electron microscopy remains the best method for the accurate identification and characterization of normal and neoplastic MEC. In human submandibular glands, two types of MECs can be distinguished in serial ultrathin sections. The dark MEC type was stellate in shape and exhibited a pronounced electron density due to numerous myofilaments with focal densities and accounted for around 76% of MEC and, furthermore, showed adenosine triphosphatase activity. The light MEC type was large and ellipsoid with a few short-thick processes and was characterized by an electron lucent cytoplasm which included scant and unevenly distributed myofilaments. They showed positive ATPase activity and accounted for only 17% of the MEC number. Transitional forms between these two types were also observed. The light MEC type may mature into the dark MEC type by means of the transitional form. In addition, clear cells were sometimes encountered between the MEC and the acinar or intercalated duct cells.[58]

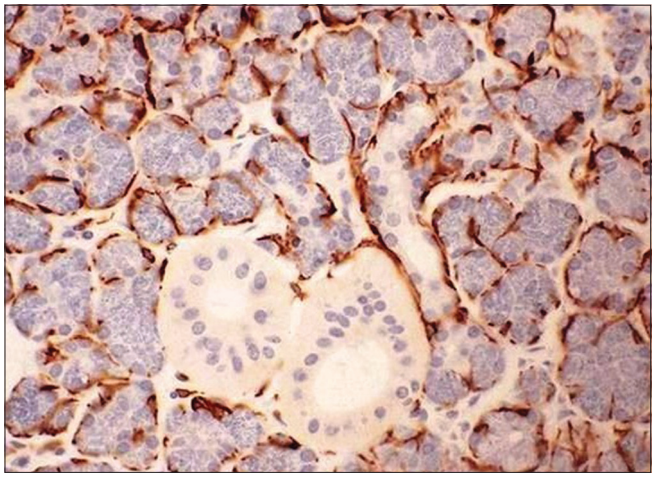


Figure 7: Demonstration of myoepithelial cells using immunohistochemistry marker cytokeratin AE1/AE3 (IHC stain, ×400) (Courtesy: http://www.pathologyoutlines.com/topic/salivaryglandssuperpage.html [last viewed on 10/04/2015])

Table 5: Types of immunohistochemical markers for myoepithelial cells

Type of IHC marker	Various markers included	Also expressed by
Smooth muscle protein markers	Alpha-SMA, SMMHC, h-caldesmon and basic calponin	Mesenchymal vasculature
Epithelial markers	Keratins 14, 5 and 17, alpha 1 beta 1 integrin, and metallothionein	Duct cells
Other mesenchymal marker	Vimentin	MECs, is expressed by the mesenchymal cells and some duct cells

Alpha-SMA: Alpha-smooth muscle actin, SMMHC: Smooth muscle myosin heavy chain, MECs: Myoepithelial cells

ROLE OF MYOEPITHELIAL CELLS IN PATHOLOGIC CONDITIONS

MECs have been implicated in various neoplastic as well as nonneoplastic disorders of the salivary glands.

Nonneoplastic disorders associated with myoepithelial cells

Lymphoreticular cell proliferation associated with atrophy of the glandular parenchyma and ductal changes ending in the so-called "epimyoepithelial islands" are characteristics of chronic recurrent (punctate) sialadenitis, sicca syndrome, Sjogren's syndrome and benign lymphoepithelial lesion. The epimyoepithelial islands are formed by metaplastic transformation of ductal epithelial and MECs. Some believe that MECs are few in number and located only around the periphery of the islands whereas majority of the workers agree that myoepithelium forms an integral part of epimyoepithelial islands.[25,59]

HISTOMORPHOGENESIS OF SALIVARY GLAND NEOPLASMS

Rationale

In pathology, histogenesis is synonymous with the "cell of origin" for a neoplasm rather than the developmental process underlying the tumor. On the other hand, morphogenesis represents the process of differentiation inherent in neoplasms and the resulting histopathology characteristic for that particular tumor.[60-62]

Histogenetic concept

A variety of histogenetic concepts for salivary gland tumors have evolved. However, the semipluripotential bicellular reserve cell hypothesis given by Eversole in 1971 is considered to be the main concept wherein it is observed that specific reserve or basal cells of the excretory and intercalated ducts or both are responsible

Table 6: Myoepithelial markers in developing and fully developed human salivary glands

Developing human salivary gland	SMA	Calponin	S100	CD29	P63	GFAP	Caldesmon	CD10
Initial bud	−	−	−	−	+	−	−	−
Pseudoglandular	+	−	−	−	+	−	−	−
Canalicular	++	+	+	+	++	−	−	−
Terminal bud	++	++	+	+	++	−	−	−
Fully developed salivary gland	++	++	++	++	++	−	−	−

SMA: Smooth muscle actin, GFAP: Glial fibrillary acidic protein

for the placement of all types of cells in the normal gland and, hence, are the sole source for neoplastic transformation. However, this theory excluded the role of cells of the striated duct.[63]

Morphogenetic concept

It is now apparent that acini and ducts including excretory, striated and intercalated ducts are associated with some form of basal/MECs.

Based on the pattern of tumor cell differentiation and tumor cell organization, it has been suggested that three basic types of tumors can develop.

a. Composed entirely or primarily of acinar or luminal epithelium
b. Composed of both luminal and basal/MECs
c. Composed only of basal/MECs.

However, this concept was modified and it was suggested that the main differentiation process underlying the histomorphology of many salivary gland tumors can be divided into five main categories as shown in Table 8.[64]

Neoplastic myoepithelial cells: Are they host friendly?

Malignant neoplasms have a near universal ability to degrade extracellular matrices, which otherwise play roles in containment of the neoplasm. Sternlicht and Barsky are credited for adding objective evidence to the subjective presumption of the tumor suppressive, or tumor ameliorative behavior of MECs. In a series of publications, these investigators have answered their hypotheses that MECs are natural tumor suppressors and resist malignant transformation and progression of the neoplasm.[23]

The MECs appear to have a modifying effect on biologic behavior of the salivary gland tumors. MECs surround benign epithelial proliferations and *in situ* carcinomas but are absent in invasive cancers. Thus, the mere presence of MECs can distinguish benign or *in situ* disease from malignant disease. Salivary gland carcinomas in which there is histopathological evidence of an active participation of MECs are generally those taking origin from the intercalated duct/secretory end piece part of the salivary duct unit. From the clinicobiological point of view, it is also those carcinomas which are regarded as low grade as judged by their relatively low ability to metastasize or a long-term progression, when compared to carcinomas without MEC participation.[23]

In the neoplastic state, myoepithelium presents with lower proliferation rates than basal type epithelial cells and secretes excess substances that inhibit tissue invasion and metastasis. These accumulated myxoid ground substances and basement membrane components contribute to an anti-invasive matrix for myoepithelial-rich SGTs as evidenced by lobulated and pushing rather than infiltrative tissue growth patterns in tumors showing MEC proliferation and prolonged survivals despite distant metastasis.[65] The various properties of MEC signifying a tumor-suppressor role are summarized in Table 9.[7,23,66]

Table 7: Immunohistochemical profile of neoplastic myoepithelium

Positive	Positive/negative	Negative
CK (AE1/AE3)	SMA	EMA
Vimentin	SMMH	CEA
S100	Cam5.2	CK7
Calponin	CK14	B72.3
p63	CK5/6	Desmin
34βE12	Maspin	HHF-35
CD10	GFAP	

CK: Cytokeratin, GFAP: Glial fibrillary acidic protein, EMA: Epithelial membrane antigen, CEA: Carcinoembryonic antigen

Neoplastic disorders associated with myoepithelial cell proliferation

The wide spectrum of morphologic presentation of salivary gland neoplasms is greatly a result of two-sided expression of myoepithelium. Table 10 summarizes the expression of MEC differentiation in the various salivary gland neoplasms.[67]

Table 8: Classification of salivary gland neoplasms

Classification of neoplasm	Sub-classification of neoplasm	Specific neoplasms	
		Benign	Malignant
Neoplasms composed of luminal and modified MECs	Histologically with apparent proteoglycan and basal lamina production	Pleomorphic adenoma Basal adenoma	Malignant mixed tumor Adenoid cystic carcinoma (cribriform)
	Histologically lacking obvious proteoglycan and basal lamina production	Basal cell adenoma Cellular pleomprphic adenoma Warthin's tumor	Basal cell adenocarcinoma Adenoid cystic carcinoma (solid/tubular) Epithelial – myoepithelial carcinoma Mucoepidermoid carcinoma Polymorphous low-grade adenocarcinoma
Neoplasms composed primarily of myoepithelial/basal cells	-	Myoepithelioma	Myoepithelial carcinoma
Neoplasms composed primarily of luminal/acinar cells	-	Canalicular adenoma Ductal papillomas Cystadenoma	Acinic cell carcinoma Salivary duct carcinoma Adenocarcinoma not otherwise specified Oncocytic carcinoma
Neoplasms composed of undifferentiated cells	-	-	Undifferentiated carcinoma Small cell carcinoma

PLEOMORPHIC ADENOMA/CARCINOMA EX PLEOMORPHIC ADENOMA

It is the most common benign salivary gland tumor in which MECs form the principal cell type. These cells can assume a variety of cytological forms such as hyaline, myxoid or epithelial cells, but they frequently occur as angular, slightly separated cells surrounding ducts or forming variably sized clusters or sheet-like regions and do not present the classical features of normal MECs. Initially, these cells are related to duct luminal cells. However, with proliferation, they are gradually separated by increasing amounts of matrix material, resulting in the development of the myxoid and chondroid areas.[29,68]

In carcinoma ex pleomorphic adenoma, the earliest changes typically consist of tumor cells replacing the normal inner duct epithelial layer leaving the normal peripherally located myoepithelial layer intact. Atypical changes within these tumors range from focal to diffuse often with multifocal areas containing carcinoma, which frequently overgrows and replaces many of the benign elements.[29]

Table 9: Properties of myoepithelial cell signifying a tumor-suppressor role

Location of MECs
Intermediary between epithelium and basement membrane
Surrounding benign and in-situ neoplasms; rarely around invasive neoplasms
Functional attributes of MECs
Synthesis and remodeling of basement membrane
Expresses laminin, nidogen, Type IV collagen, and perlecan
Induction of epithelial morphogenesis
Secretes growth factors and cytokines (BFGF, TGF α and interleukin 6)
Accumulation of extracellular matrix
Produces interstitial collagen and chondroitin sulfate and Proteoglycan
Effects on surrounding tissue in the microenvironment
Downregulation of MMP gene expression in cancer cells and fibroblasts
Expression and accumulation of high amounts of tumor suppressors and proteinase inhibitors
Secretes high levels of maspin (an inhibitor of tumor growth and invasion)
Secretes tissue inhibitor of metalloproteinase-1, protease nexin II, α1-antitrypsin
Low-level secretion of matrix-degrading proteinases
Absence of stromelysin-1
Inhibition of angiogenesis

MECs: Myoepithelial cells, MMP: Matrix metalloproteinase, TGF α: Transforming growth factor α, bFGF: Basic fibroblast growth factor

MYOEPITHELIOMA/MYOEPITHELIAL CARCINOMA

Myoepitheliomas are a type of pleomorphic adenoma in which neoplastic MECs exclusively or predominantly proliferate. Cytologically, tumor cells can be either spindle-shaped, epithelioid or plasmacytoid or clear cells. Occasionally, however, myxoid and chondroid matrix may also form a significant part of the histology. Predomination of any one cell type, not necessarily a homogenous population of tumor cells, underlies a particular histomorphologic form.[35,69]

The cells in myoepithelial carcinoma resemble tumor cells in benign myoepithelioma and the MECs in pleomorphic adenoma; however, they usually demonstrate increased mitotic activity and cytologic pleomorphism, large and more vesicular nuclei and more prominent nucleoli.[70]

BASAL CELL ADENOMA/BASAL CELL ADENOCARCINOMA

It has been found that although basal cell adenoma subtypes appear microscopically basaloid and monomorphic in architectural patterns compared with pleomorphic adenoma, periductal, epithelioid and spindled (stromal-like) MECs contribute to the proliferation of these tumors. The MECs in these tumors are truly neoplastic rather than entrapped normal cells for the following reasons. First, the morphologic heterogeneity of stained cells (periductal, spindled and epithelioid) departs from that of normal myoepithelium. Second, the MECs highlighted by the monoclonal antibodies form an integral part of the tumors and are not merely situated at the periphery.[71]

Other than invasion, basal cell adenocarcinomas are morphologically very similar to the benign counterpart.[7]

Table 10: Expression of myoepithelial cells in various salivary gland neoplasms

Benign neoplasms			Malignant neoplasms		
Predominant MCD	**Partial MCD**	**No MCD**	**Predominant MCD**	**Partial MCD**	**No MCD**
Pleomorphic adenoma Myoepithelioma	Basal cell adenoma	Canalicular adenoma Warthin's tumor Oncocytoma Sebaceous adenoma Ductal papilloma	Adenoid cystic carcinoma Myoepithelial carcinoma Epithelial – myoepithelial carcinoma Carcinoma ex pleomorphic adenoma	Basal cell adenocarcioma PLGA mucoepidermoid carcinoma	Acinic Cell carcinoma Salivary duct carcinoma Hylinizing clear cell carcinoma Squamous cell carcinoma Oncocytic Carcinoma

MCD: Myoepithelial cell differentiation

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma is a basaloid tumor consisting of epithelial and MECs in variable morphologic configurations. The complexity underlying the histologic features of adenoid cystic carcinoma is based on the frequency and prominence of ductal structures, basal/myoepithelial cells and intercellular matrix materials resulting in the formation of three histologic variants such as cribriform, solid and tubular.[29]

EPITHELIAL - MYOEPITHELIAL CARCINOMA

A malignant tumor that comprises variable proportions of two cell types, which typically form duct-like structures is epithelial-myoepithelial carcinoma. The two cell types are arranged as an inner layer of darker cells that represents the intercalated duct epithelial component and an outer layer of cells with clear, glycogen-rich cytoplasm that represents the myoepithelial component, the proportions of which may vary from one neoplasm and in different fields within the same tumor.[29]

POLYMORPHOUS LOW GRADE ADENOCARCINOMA (PLGA)

A malignant epithelial tumor is characterized by cytologic uniformity, morphologic diversity, an infiltrative growth pattern and low metastatic potential. There is a significant, if not predominant, myoepithelial differentiation in these tumors denoted by the presence of analogous histologic patterns (architectural arrangements, myxoid and hyalinized matrices) as seen in myoepitheliomatous zones of pleomorphic adenoma and adenoid cystic carcinoma.[67]

MUCOEPIDERMOID CARCINOMA

Current classifications of SGTs separate mucoepidermoid carcinoma from other neoplasms on the basis of a number of histological features, in particular, the lack of participation of neoplastic MECs. However, ultrastructural examination of low- and intermediate-grade mucoepidermoid carcinomas and pleomorphic adenomas reveals many common organizational and cellular features. The relationship of intermediate cells to the luminal cells in mucoepidermoid carcinomas is of prime importance, which is remarkably similar to that seen between modified MECs and luminal cells in pleomorphic adenomas. These results suggest that intermediate cells of mucoepidermoid carcinoma are the counterpart of the modified MECs of pleomorphic adenoma.[33]

SUMMARY AND CONCLUSION

In this article, we reviewed the various aspects of MECs in normal conditions as well the morphologic diversity of these cells in various pathologic conditions. It can be observed that the neoplastic counterpart of these cells shows certain morphological and architectural alterations which are responsible for variations in the histopathologic patterns of the various salivary gland neoplasms. Thus, an evaluation of SGTs based on an accurate recognition of myoepithelial differentiation (as described), their various morphologic and immunophenotypic expressions is essential in establishing a definitive role of myoepithelium in salivary gland neoplasm.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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