Pathophysiology of myoepithelial cells in salivary glands

Amisha Ashok Kumar Shah, Aamera Farouq Mulla, Mrinal Mayank

Department of Oral Pathology and Microbiology, M.A. Rangoonwala College of Dental Sciences and Research Centre, Azam Campus, Pune, Maharashtra, India

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].

HISTORICAL INTRODUCTION

A brief history about the various terminologies used for these cells is shown in Table 1.

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].

DEVELOPMENT OF SALIVARY GLAND MYOEPITHELIAL CELLS

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

DISTRIBUTION

MECs are located beneath the basement membrane of the terminal portion of most exocrine glands including...
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 \( \alpha \) 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.\[10\]

**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 \(\alpha\)1-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

### Table 2: Stages in development of myoepithelial cell

| Phase of development                  | Stage in fetal life (weeks) | Features                                                                                                                                 |
|---------------------------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Early development stage               | 10–18                      | Initiation                                                                                                                                 |
| Early intermediate developmental stage | 19–24                      | Structural changes. MECs express actin filaments before the maturation of the acinar and ductal luminal cells takes place                  |
| Late intermediate developmental stage | 25–32                      | Maturation. Cells get further flattened and dendritic at the basal portions of the acinar and intercalated duct structures                  |
| Late developmental stage              | 33–40                      | Proliferation. MECs increase in number and develops contractile properties. Cells which first developed in the acinar and intercalated duct areas move toward the excretory ducts through the basal portions of the duct. |

MECs: Myoepithelial cells

![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)](image)
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\[22,27,28\].

**NEOPLASTIC MYOEPIHELIAL 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.\[29\]

**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: \[20-32\]

- 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].\(^{[7,29]}\)

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

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 | ![Image](image1.png) |
| Epitheloid         | Polygonal with vesicular nuclei and ample cytoplasm | ![Image](image2.png) |
| Clear              | Cells contain clear cytoplasm due to glycogen    | ![Image](image3.png) |
| Spindle            | Cells are elongated, fusiform with pale cytoplasm | ![Image](image4.png) |
| Plasmacytoid (hyaline) | Cells have bright eosinophilic cytoplasm with eccentric nuclei | ![Image](image5.png) |

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 | ![Diagram of myxoid pattern] |
| Solid pattern (nonmyxoid)  | Cells in nests, sheets are seen with intervening hyalinized matrix generally seen in basal cell adenoma       | ![Diagram of solid pattern] |
| Reticular pattern          | Anastomozing pattern predominantly of epitheloid-MECs intervened by extracellular material commonly seen in canalicular adenoma | ![Diagram of reticular pattern] |
| Microcystic/pseudocystic pattern | Variable sized and loose cystic spaces formed by accumulating myxoid matrix within nests of tumor cells | ![Diagram of microcystic/pseudocystic pattern] |
| Cribriform/pseudoglandular pattern | Clusters of epitheloid cell form cribriform structures and pseudolumen due to their myxoid matrix production commonly associated with adenoid cystic carcinoma | ![Diagram of cribriform/pseudoglandular pattern] |

MECs: Myoepithelial cells. (Courtesy: Dardick I. Color Atlas/Text of Salivary of Salivary Gland Tumor Pathology. 1st ed. New York: 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]

**ROLE OF MYOEPIHELIAL 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 for the development of various epithelial neoplasms of the salivary glands.

**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 |

**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]

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 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 |
| p53 | CK5/6 | Desmin |
| 34BE12 | Maspin | HHF-35 |
| CD10 | GFAP |

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

Table 8: Classification of salivary gland neoplasms

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

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]

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

| Location of MECs                      | Functional attributes of MECs                                                                 |
|--------------------------------------|------------------------------------------------------------------------------------------------|
| Intermediary between epithelium and basement membrane | Synthesis and remodeling of basement membrane                                               |
| Surrounding benign and in-situ neoplasms; rarely around invasive neoplasms | 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 metallocproteinase-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

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

| Benign neoplasms | Partial MCD | No MCD | Malignant neoplasms | Partial MCD | No MCD |
|------------------|-------------|--------|--------------------|-------------|--------|
| Pleomorphic adenoma | Basal cell adenoma | Canalicularenoma | Adenoid cystic carcinoma | Basal cell adenocarcinoma | Acinic Cell carcinoma |
| Myoepithelioma   | Warthin’s tumor | Myoepithelial carcinoma | Epithelial – myoepithelial carcinoma | PLGA | Salivary duct carcinoma |
|                  | Oncocytoma   | Sebaceous adenoma | Carcinoma ex pleomorphic adenoma | mucopidermoid carcinoma | Hyalinizing clear cell carcinoma |
|                  | Ductal papilloma | | | | Squamous cell 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]

MUCOEPOIDERMOID 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.[43]

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.

REFERENCES
1. Nanci A. Ten Cate’s Oral Histology: Development, Structure, and Function. 8th ed. Philadelphia: Elsevier Mosby; 2012.
2. Redman RS. Myoepithelium of Salivary Glands. Microscopy Research and Technique 1994;1(27):25-45.
3. Travill AA, Hill MF. Histochemical demonstration of myoepithelial cell activity. Q J Exp Physiol Cogn Med Sci 1963;48:423-6.
4. Garrett JR, Ekström J, Anderson LC editors. Glandular mechanisms of salivary secretion. 1st ed. Basel: Karger publications; 1998.
5. Batsakis JG, Kraemer B, Scuibba JJ. The pathology of head and neck tumors: The myoepithelial cell and its participation in salivary gland neoplasia, Part 17. Head Neck Surg 1983;5:222-33.
6. Nirmalkumar H, Jagannathan N. Myoepithelial cells: Revisited – Review. Ann RSCB. 2013;XVIII: 9-15.
7. Savera AT, Zarbo RJ. Defining the role of myoepithelial in salivary gland neoplasia. Adv Anat Pathol 2004;11:69-85.
8. Raubenheimer EJ. The myoepithelial cell: Embryology, function, and proliferative aspects. Crit Rev Clin Lab Sci 1987;25:161-93.
9. Garrett JR, Emmelin N. Activities of salivary myoepithelial cells: A review. Med Biol 1979;57:1-28.
10. Garrett JR, Parsons PA. Alkaline phosphatase and myoepithelial cells in the parotid gland of the rat. Histochem J 1973;5:463-71.
11. Cope GH, Pratten MK, Williams MA. Correlative morphological and biochemical study of the effects of isoprenaline on the organelle and membrane content of the rabbit parotid gland. Histochem J 1976;8:403-18.
12. Linzell JL. Some observations on the contractile tissue of the mammary glands. J Physiol 1955;130:257-67.
13. Young JA, Van Lennep EW. Morphology and physiology of salivary myoepithelial cells. Int RevPhysiol 1977;12:105-25.
14. Tandler B, Denning OR, Mandel ID, Kutscher AH. Ultrastructure of human labial salivary glands 3. Myoepithelium and ducts. J Morphol 1970;130:227-45.
15. Tamarin A. Myoepithelium of the rat submaxillary gland. J Ultrastruct Res 1966;16:320-38.
16. Nagai T, Nagai M. Scanning electron microscopy of the human submandibular gland. Arch Otorhinolaryngol 1985;241:265-66.
17. Ruby JR. Ultrastructure of the parotid gland of the nine-banded armadillo. Anat Rec 1978;192:389-405.
18. Toto PD, Hsu DJ. Product definition of pleomorphic adenoma of minor salivary glands. J Oral Pathol 1985;14:818-32.
19. Bogart Bl. The fine structural localization of alkaline and acid phosphatase activity in the rat submandibular gland. J Histochem Cytochem 1968;16:572-81.
20. Yoshihara T, Kanda T, Kaneko T. A cytochemical study on the salivary gland pleomorphic adenoma (mixed tumor) and the fetal and adult salivary gland. Arch Otorhinolaryngol 1984;240:231-8.
21. David R, Buchner A. Elastosis in benign and malignant salivary gland tumors. A histochemical and ultrastructural study. Cancer 1980;45:2301-10.
22. Sternlicht MD, Safarian S, Rivera SP, Barsky SH. Characterization of the
extracellular matrix and proteinase inhibitor content of human myoepithelial tumors. Lab Invest 1996;74:781-96.

23. Sternlicht MD, Barsky SH. The myoepithelial defense: A host defense against cancer. Med Hypotheses 1997;48:37-46.

24. Shear M. The structure and function of myoepithelial cells in salivary glands. Arch Oral Biol 1966;11:769-80.

25. Raubenheimer EJ, van Nickerk JP, Hauman CH. Salivary myoepithelium: Distribution, structure, functions and pathologic proliferations. J Dent Assoc S Afr 1987;42:631-7.

26. Chaudhry AP, Cutler LS, Yamane GM, Labay GR, Sunderraj M, Manak JR Jr. Ultrastructure of normal human parotid gland with special emphasis on myoepithelial distribution. J Anat 1987;152:1-11.

27. Tandler B. Structure of the human parotid and submandibular glands. In: Sreebny LM, editor. The Salivary System. 1st ed. Boca Raton FL: CRC Press; 1996.

28. Bois RM. The organization of the contractile apparatus of vertebrate smooth muscle. Anat Rec 1973;177:61-77.

29. Dardick I. Color Atlas/Text of Salivary of Salivary Gland Tumor Pathology. 1st ed. New York: Igaku-Shoin Medical Publishers, Inc.; 1996.

30. Dardick I, Ostrynski VL, Ekem JK, Leung R, Burford-Mason AP. Immunohistochemical and ultrastructural correlates of muscle-actin expression in pleomorphic adenomas and myoepitheliomas based on comparison of formalin and methanol fixation. Virchows Arch A Pathol Anat Histopathol 1992;421:95-104.

31. Erlander MA, Cardon-Cardo C, Higgins P.J. Histogenesis of benign pleomorphic adenoma (mixed tumor) of the major salivary glands. An ultrastructural and immunohistochimical study. Am J Surg Pathol 1984;8:803-20.

32. Dardick I. Myoepithelium: Definitions and diagnostic criteria. Ultrastruct Pathol 1995;19:335-45.

33. Dardick I, Gliniecki MR, Heathcote JG, Burford-Mason A. Comparative histogenesis and morphogenesis of mucoepidermoid carcinoma and pleomorphic adenoma. An ultrastructural study. Virchows Arch A Pathol Anat Histopathol 1990;417:405-17.

34. Dardick I, van Nostrand AW. Myoepithelial cells in salivary gland tumors – Revisited. Head Neck Surg 1985;7:395-408.

35. Dardick I, Thomas MJ, van Nostrand AW. Myoepithelioma – New concepts of histology and classification: A light and electron microscopic study. Ultrastruct Pathol 1989;13:187-224.

36. Dardick I, Cavel S, Boivin M, Hoppe D, Parks WR, Stinson J, et al. Salivary gland myoepithelioma variants. Histological, ultrastructural, and immunocytochemical features. Virchows Arch A Pathol Anat Histopathol 1989;416:25-42.

37. Sarkar K, Kallenbach E. Myoepithelial cells in carcinoma of human breast. Am J Pathol 1986;49:301-7.

38. Puchtler H, Leblond CP. Histochemical analysis of cell membranes and histochemical reactions in the salivary glands of cat, dog and man, with particular reference to the myoepithelial cells. Histochemie 1971;24:214-29.

39. Leblond CP, Puchtler H, Clermont Y. Structures corresponding to terminal bars and terminal web in many types of cells. Nature 1960;186:784-7.

40. Auger DW, Harrison JD. Ultrastructural phosphorylase cytochemistry of the intercalary ducts of the parotid and submandibular salivary glands of man. Arch Oral Biol 1982;27:79-81.

41. Cutler LS, Chaudhry A, Innes DJ Jr. Ultrastructure of the parotid duct. Cytochemical studies of the striated duct and papillary cystadenoma lymphomatosum of the human parotid gland. Arch Pathol Lab Med 1977;101:240-2.

42. Garrett JR, Harrison JD. Alkaline-phosphatase and adenosine-triphosphatase histochemical reactions in the salivary glands of cat, dog and man, with particular reference to the myoepithelial cells. Histochemistry 1971;24:214-29.

43. Harrison JD. Cystic adenoma of a minor salivary gland: A histochemical study. J Pathol 1973;114:29-38.

44. Harrison JD. Minor salivary glands of man: Enzyme and mucousubstance histochemical studies. Histochem J 1974;6:633-47.

45. Innes DJ Jr., Cutler LS. Phosphatase enzymes. Cytochemical study of pleomorphic adenoma and normal human salivary glands. Arch Pathol Lab Med 1978;102:90-4.

46. Ogawa Y. Immunocytochemistry of myoepithelial cells in the salivary glands. Prog Histochem Cytochem 2003;38:343-426.