Review Article

Myoepithelial cells: Current perspectives in salivary gland tumors

C. Pramod Redder, V. Suresh Kandagal, Nupura Vibhute, Pramod S. Ingaleshwar[1], Sharan J. Shetty[1], Sameer Ahamad[2]

Department of Oral Pathology and Microbiology, School of Dental Sciences, Krishna Institute of Medical Sciences University, Karad, Maharashtra, [1]Department of Oral Pathology and Microbiology, A. J. Institute of Dental Sciences, Mangalore, Karnataka, [2]Department of Oral Pathology and Microbiology, Kunhitharuvai Memorial Charitable Trust Dental College, Calicut, Kerala, India

ABSTRACT

Myoepithelial cells are normal constituent of the salivary acini and smaller ducts, and are found between the epithelial cells and the basement membrane. Microscopic examination shows that myoepithelial cells are thin and spindle-shaped and situated between the basement membrane and epithelial cells. Ultrastructurally they possess a number of cytoplasmic processes that extend between and over the acinar and ductal-lining cells. They display features of both smooth muscle and epithelium, such as numerous microfilaments with focal densities in the cytoplasmic processes, and desmosomes which attach the myoepithelial to the epithelial cells. Neoplastic myoepithelial cells in both benign and malignant tumors can take several forms, including epithelioid, spindle, plasmacytoid, and clear, and this variability largely accounts for difficulties in histopathological diagnosis. This review article highlights the role of myoepithelial cells in salivary gland tumors.

Key words: Basal cells, luminal cells, myoepithelial cells, salivary gland tumor

INTRODUCTION

Myoepithelial cells (sometimes referred to as myoepithelium) are cells usually found in glandular epithelium as a thin layer above the basement membrane but generally beneath the luminal cells. They are found in the sweat glands, mammary glands, lacrimal glands, and most importantly in salivary glands. Myoepithelial cells are stellate-shaped and also known as basket cells. Each cell consists of a cell body from which four to eight processes radiate and embrace the secretory unit. Myoepithelial cells may be of ectodermal or endodermal in origin.[1]

Myoepithelial cells are a normal constituent of the major and minor salivary glands. In 1898, Zimmerman first described the salivary gland myoepithelium. Myoepithelial cells are ectodermal in origin and envelope glandular/acinar and ductal elements of salivary gland. They are plentiful in the salivary acini and intercalated ducts, but much less so in the larger excretory ducts of the major glands.[2]

Microscopic examination of these cells show that they are thin and spindle shaped and situated between the basement membrane and epithelial cells. Ultrastructurally they possess a number of cytoplasmic processes that extend between and over the acinar and ductal lining cells.[3] They display features of both smooth muscle and epithelium, such as numerous microfilaments with focal densities in the cytoplasmic processes, and desmosomes which attach them to the epithelial cells [Figure 1].

ROLE OF MYOEPITHELIAL CELLS

During embryonic development they are involved in branching morphogenesis of developing salivary gland and promotion of epithelial cell differentiation. Myoepithelial cells are responsible for extracellular matrix synthesis especially basement membrane materials.

Their functions include contraction when the gland is stimulated to secrete, compressing or reinforcing the

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Address for correspondence: Dr. Suresh Kandagal V., Department of Oral Medicine and Radiology, School of Dental Sciences, Krishna Institute of Medical Sciences University, Karad, Satara, Maharashtra, India. E-mail: dr.suri88@gmail.com

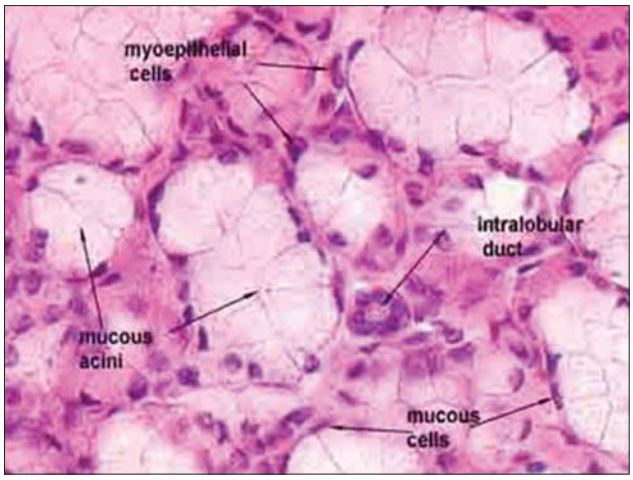

Figure 1: Photomicrograph showing myoepithelial cells

underlying parenchymal cells, thus aiding in the expulsion of saliva and preventing damage to the other cells. Intermediary location between stroma and luminal cells plays a crucial role (paracrine role) and regulates electrolyte exchange. They also may aid in the propagation of secretory and other stimuli.[4]

Recent studies show that myoepithelial cells have a tumor suppressor role as they exert a paracrine anti-invasive role by promoting epithelial differentiation, synthesis of basement membrane secreting proteinase inhibitors, and inhibiting angiogenesis.[4,5]

Salivary glands have the most histologically heterogeneous group of tumors and the greatest diversity of morphological features among their cells and tissues.[4] Neoplastic myoepithelium is considered a key cellular participant in morphogenetic processes, responsible for variable histological appearances of many salivary gland tumors. But controversy still exists concerning its participation in certain tumors.[2]

The following review highlights this versatility or spectrum of morphological appearances of myoepithelial cells. The varied role of myoepithelial cells in the pathogenesis of the various salivary gland tumors is also discussed.

IDENTIFICATION OF MYOEPITHELIAL CELLS

In view of the pivotal role played by these myoepithelial cells in various salivary gland neoplasms, their identification and detection is an important link in the study of salivary gland tumors. The common developmental origin of myoepithelial cells with the basal cells of the larger ducts is displayed in the mature glands by shared structural and immunohistochemical features, although most such basal cells do not have the distinguishing features of myoepithelial cells, such as myofibrils. Although myoepithelial cells can be identified by light microscopy through enzyme histochemistry and special stains and immunohistochemistry for their myofibrils, these techniques can be misleading in salivary gland neoplasms. Thus, the most reliable means of identifying neoplastic myoepithelial cells is with a combination of histochemistry and electron microscopy.

In routinely stained histopathological section, they are difficult to identify as only the nucleus is seen. Histochemical stains such as phosphotungstic acid hematoxylin and iron hematoxylin, levanol-fast cyanine (Coomasie Blue), silver impregnation method are used for better identification.[6]

DIFFERENT MARKERS OF MYOEPITHELIAL CELLS

Alpha-smooth muscle actin (aSMA), calponin, smooth muscle myosin heavy chain (SMMHC),[7] h-caldesmon,[8] S-100 protein,[9] and cytokeratins (subtype 14).[10] Maspin,[11] p63,[12] and CD10[13] have recently been described as markers of breast myoepithelial cells, and may have a role in identifying their salivary equivalents. CD10 is useful in differentiating between normal and neoplastic salivary myoepithelial cells.[13]

MORPHOLOGICAL SPECTRUM OF NEOPLASTIC MYOEPITHELIUM

The complex morphological patterns of neoplastic myoepithelium result from an intricate interplay of three fundamental characteristics of neoplastic myoepithelial cells, namely:

1. Cytological differentiation
2. Extracellular matrix production
3. Architectural patterns

CYTOLOGICAL DIFFERENTIATION

Myoepithelial cells have the potential for divergent differentiation resulting in different morphological cell types. The various guises displayed by myoepithelial cells are:

a. Angulate/basaloid cells: These cells show small hyperchromatic nuclei with faint eosinophilic cytoplasm.
b. Epitheloid cells: These cells show polygonal with vesicular nuclei and ample cytoplasm.
c. Clear cells: These cells contain clear cytoplasm due to glycogen.
d. Spindle cells: These cells are elongated, fusiform with pale cytoplasm.
e. Plasmacytoid (hyaline cells): These cells have bright eosinophilic cytoplasm with eccentric nuclei.

Most tumors with myoepithelial cell differentiation reveal more than one cell type, this morphological heterogeneity is a consistent feature and reliable clue of myoepithelial differentiation. These cells can undergo metaplastic changes such as chondroid, squamous, oncocytic, etc.[4-6]

EXTRACELLULAR MATRIX PRODUCTION

In normal state, myoepithelium produces basement membrane components and extracellular matrix. Neoplastic myoepithelium modify the matrix synthesizing property production of large amount of basement membrane (BM) and non-basement membrane elements. Dominant component of non BM matrix is chondroitin sulfate which appears bluish gray and myxochondroid material which is alcian blue-positive.

Others are eosinophilic hyalinised material representing BM related (type IV collagen, laminin) and interstitial matrix (fibronectin, type I, II collagen). True nature of extracellular matrices particularly myxoid material identification is important in salivary gland tumor identification. For example, collection of such material and abundant basal lamina is seen in many salivary gland tumors including pleomorphic adenoma, Ca ex-pleomorphic adenoma, myoepithelioma, terminal duct carcinoma, epithelial myoepithelial carcinoma, and adenocarcinoma.[1,4]

ARCHITECTURAL PATTERNS

The diverse architectural patterns due to myoepithelial cells have been described by Dardick as follows:

1. Myxoid pattern in which tumor cells are loosely and randomly distributed due to production of abundant chndromyxoid matrix.
2. Solid pattern (non-myxoid) in which cells in nests, sheets are seen with intervening hyalinized matrix
3. Reticular pattern shows anastomozing pattern predominantly of epitheloid-myoepithelial cells intervened by extracellular material
4. Microcystic/Pseudocystic pattern shows variable sized and loose cystic spaces formed by accumulating myxoid matrix within nests of tumor cells
5. Cribriform/pseudoglandular pattern in which clusters of epitheloid cell form cribriform structures and pseudolumen due to their myxoid matrix production.[4,6]

ROLE OF MYOEPITHELIAL CELLS IN SPECIFIC SALIVARY GLAND TUMORS

Pleomorphic adenoma (PA) and myoepithelioma

Both tumors are closely related as myoepithelial cell is the primary proliferating cell in both the tumors. Previously, any benign salivary gland tumor with myxochondroid matrix was labeled as PA and the term myoepithelioma was reserved for tumors that were solidly composed of spindle cells or plasmacytoid myoepithelial cells. However, it is now well accepted that myoepithelial differentiation is predominant in these tumors and responsible for various "mesenchymal" components and their morphological diversity. The acini, ducts including excretory, striated and intercalated ducts are associated with some form of basal and/or myoepithelial cell. If one considers the combination of ductal, luminal or acinar cells, and basal or myoepithelial cells as a basic of normal gland, then neoplasia also reflects the cellular makeup of this unit or any individual component [Table 1].[14]

Basal cell adenoma

In 1967, Kleisasser/Klein first described basal cell adenoma. Owing to lack of myxochondroid component and homology of tumors cells these were considered monomorphic. The basis of separating these neoplasms from PA was lack of myoepithelial differentiation. Myoepithelial participation in all variants of basal cell adenoma has been documented.

Another evidence of myoepithelial participation in basal cell adenoma is presence of hyalinized matrix. Small amounts of myxoid matrix exist and neoplastic myoepithelium in these tumors primarily produce BM-related and interstitial matrix. This forms the typical hyaline droplets in basal cell adenoma.

Table 1: MCD in salivary gland tumors

Benign salivary gland tumors[1,2,4,5]			Malignant salivary gland tumors[1,2,4,5]		
No MCD	**Partial MCD**	**Predominant MCD**	**No MCD**	**Partial MCD**	**Predominant MCD**
Canalicular adenoma, Warthins tumor Oncocytoma, Sebaceous adenoma, Ductal papilloma	Basal cell adenoma	Pleomorphic adenoma, Myoepithelioma	Acinic cell carcinoma, Salivary duct carcinoma, Hyalinizing clear cell carcinoma, Squamous cell carcinoma, Oncocytic carcinoma	Basal cell adenocarcinoma, Polymorphous low-grade carcinoma, Mucoepidermoid carcinoma	Adenoid cystic carcinoma, Myoepithelial carcinoma, Epithelial-myoepithelial carcinoma, Myoepithelial carcinoma Ex-pleomorphic adenoma

MCD=Myoepithelial cell differentiation

It is believed that salivary gland adenomas/myoepithelioma can be viewed as neoplasms lying on a spectrum histologically separable by the dimensions of the participating cell types and type of extracellular matrix by neoplastic cells.[14,15]

Adenoid cystic carcinoma

Adenoid cystic carcinoma displays a dual epithelial and myoepithelial differentiation evident in three patterns: Cribriform, Tubular, and Solid. Myoepithelial cells are present as small basaloid/angulate cells in periductal location or in cribriform structures. Solid variant displays scattered or peripheral basaloid myoepithelial cells in small nests/sheets. Both types of myoepithelial matrices are seen in ACC giving rise to the characteristic collagenous/hyalinized stroma and bluish myxoid material associated with cribriform structures. Myoepithelial component can display clear cell change here similar to that seen in epithelial Myoepithelial carcinoma.[16]

Epithelial myoepithelial carcinoma

This lesion has ductal epithelial myoepithelial differentiation as prominent nodular growth pattern with epithelial tubules cuffed by clear myoepithelial cells. Bimorphic epithelial myoepithelial carcinomas are similar to ACC in their staining of outer clear cells with myoepithelial markers in conjunction with vimentin/cytokeratins.

When it is predominantly myoepithelial its distinction from other primary clear cell carcinomas, clear cell myoepithelial carcinoma and hyalinizing clear cell carcinoma is difficult.[17,18]

Polymorphous low-grade adenocarcinoma

Immunohistochemical and ultrastructural studies in favor or against myoepithelial participation have been reported for this lesion. Focal staining with smooth muscle markers has been detected in this lesion. There is said to be significant if not predominant myoepithelial differentiation denoted by presence of analogous histological pattern (myxoid hyalinized matrix) as in myoepitheliomatous zone of pleomorphic adenoma and adenoid cystic carcinoma.[3,4]

Mucoepidermoid carcinoma

Dardick and colleagues reported that MEC have an organized pattern involving luminal epithelial cells surrounded by intermediate cells, which are considered to be modified myoepithelial cells. The histogenesis of MEC regarding the role of myoepithelial cell is controversial. Some researchers believe that this neoplasm originates from reserve duct cell either excretory or intercalated duct. Others believe that myoepithelial cells have a role in the histogenesis. Histogenesis is linked to the nature of the so called intermediate cells.

Dardick *et al.*, (1984) proposed two basic cell types in histogenesis of MEC: The luminal epithelial and peripheral "modified" myoepithelial cells. Luminal epithelial cells differentiated into mucous producing cells. The modified myoepithelial cells corresponded to intermediate cells and were capable of squamous metaplasia.

It has been proposed that undifferentiated stem cells serve as pluripotential reserves which give rise to various cell types in MEC. Reserve cells in acinar intercalated duct system give rise to serous/mucoid and myoepithelial cell population. Reserve cells in proximal duct system (striated/excretory) differentiated into myoepithelium, intermediate cells, squamous/epidermoid cells, and mucous-producing cell lines.[3]

Myoepithelial cells in non-neoplastic disease: Benign lymphoepithelial lesion

The role of myoepithelial cells in this lesion is controversial. The development of BLL begins with infiltrates of lymphocytes that expand to replace the glandular epithelium, associated with hyperplasia and metaplasia of ductal epithelium, resulting in epimyoepithelial islands.

In early ultrastructural study several kinds of cells were seen in epimyoepithelial islands but no myoepithelial cells.

Other authors described three stages in development of the islands. Islands initially formed from intercalated duct cells around duct lumen. Myoepithelial cells arranged peripherally surrounded by basement membrane complex. This is followed by destruction of the duct epithelium proliferation of myoepithelium and infiltration by lymphocytes. The final stage is hyaline transformation. Some studies suggested that myoepithelial cells were seen only in early stages of island development.[4]

CONCLUSIONS

Thus, neoplastic myoepithelial cells are considered to be a key cellular participant in morphogenetic process responsible for various histological appearances of salivary gland tumors. Nevertheless, controversy still exists concerning its participation in some salivary gland neoplasms. This has been due to the difficulty in fully characterizing the wide spectrum of morphological and immunophenotypic expressions of neoplastic myoepithelium compared with normal counterpart. Understanding the myoepithelial cells has thus important implications for clarifying diagnostic problems and improving the classification of salivary gland tumors.

REFERENCES

1. Gnepp DR. Diagnostic Surgical Pathology of the Head and Neck. Philadelphia: W. B. Saunders Co; 2001.

2. Dardick I, Daya D, Hardie J, Van Nostrand AW. Mucoepidermoid carcinoma: Ultrastructural and histogenetic aspects. J Oral Pathol 1984:13:342-58.
3. 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.
4. Ellis GL. Surgical Pathology of Salivary Glands. 1st ed, vol. 25. Philadelphia: Elsevier Health Sciences; 1991.
5. Batsakis JG, Kraemer B, Sciubba 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. Ellis GL, Auclair PL, Gnepp DR. Surgical Pathology of the Salivary Glands. In the Major Problems in Pathology Series. vol. 25. Philadelphia: W.B. Saunders Co; 1991.
7. Furuse C, Sousa SO, Nunes FD, Magalhaes MH, Araujo VC. Myoepithelial cell markers in salivary gland neoplasms. Int J Surg Pathol 2005;13:57-65.
8. Ellis GL, Auclair PL. Atlas of Tumor Pathology: Third series, fascicle 17. Tumors of the Salivary Glands. Washington DC: Armed Forces Institute of Pathology; 1996. p. 1-26.
9. Prasad AR, Savera AT, Gown AM, Zarbo RJ. The myoepithelial immunophenotype in 135 benign and malignant salivary gland tumors other than pleomorphic adenoma. Arch Pathol Lab Med 1999;123:801-6.
10. Foschini M, Scarpellini F, Gown AM, Eusebi V. Differential expression of myoepithelial markers in salivary, sweat and mammary glands. Int J Surg Pathol 2000;8:29-37.
11. Jones H, Moshtael F, Simpson RH. Immunoreactivity of alpha smooth muscle actin in salivary gland tumours: A comparison with S100 protein. J Clin Pathol 1992;45:938-40.
12. Reis-Filho JS, Milanezi F, Silva P, Schmitt FC. Maspin expression in myoepithelial tumors of the breast. Pathol Res Pract 2001;197:817-21.
13. Barbareschi M, Pecciarini L, Cangi MG, Macrì E, Rizzo A, Viale G, *et al*. p63, a p53 homologue, is a selective nuclear marker of myoepithelial cells of the human breast. Am J Surg Pathol 2001;25:1054-60.
14. Hirano T, Kashiwado I, Suzuki I, Yoshihiro T, Yuge K, Asano G. Immunohistopathological properties of pleomorphic adenoma in salivary gland. Nihon Ika Daigaku Zasshi 1990;57:172-9.
15. Zarbo RJ, Prasad AR, Regezi JA, Gown AM, Savera AT. Salivary gland basal cell and canalicular adenomas: Immunohistochemical demonstration of myoepithelial cell participation and morphogenetic considerations. Arch Pathol Lab Med 2000;124:401-5.
16. Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. Cancer 1984;54:1062-9.
17. Simpson RH, Clarke TJ, Sarsfield PT, Gluckman PG. Epithelial-myoepithelial carcinoma of salivary glands. J Clin Pathol 1991;44:419-23.
18. Hagiwara T, Yoshida H, Takeda Y. Epithelial-myoepithelial carcinoma of a minor salivary gland of the palate: A case report. Int J Oral Maxillofac Surg 1995;24:160-1.

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