Review Article

DOI: 10.7860/JCDR/2015/11372.5707

Dentistry Section

Myoepithelial Cells (MEC) of the Salivary Glands in Health and Tumours

RAVI TEJA CHITTURI [1], V. VEERAVARMAL[2], R. MADHAVAN NIRMAL[3], B. VENKAT RAMANA REDDY[4]

ABSTRACT

Myoepithelial cells (MEC) are found in the secretory units of many mammalian exocrine glands such as mammary, sweat, lacrimal and salivary glands. They are interposed between the secretory cells and the basal lamina. Immunohistochemically they are found to contain keratin intermediate filaments and are, therefore, considered to have an epithelial origin but at the same time they contain a large number of myofilaments which represent a massive expression of contractile proteins such as actin, myosin, calponin and caldesmon. Thus have smooth muscle like property also and hence the name. Numerous functions of MEC have been described, the most important of them being important for contraction of the glands and recently it has been found to prevent tumour progression. It should be noted that the diversity in the occurrence and dilemma regarding the pathogenesis of salivary gland tumours is due to lack in uniformity regarding the cells participating in its oncogenesis, especially the MEC. Also proper and extensive studies regarding MEC are very limited and thus have posed difficulty for a pathologist to understand this cell. In this review we try to bring about a thorough description of this cell in both physiological and pathological aspects.

Keywords: Functions, Immunohistochemical markers,Myoepithelial cell expression in salivary gland tumours

INTRODUCTION

In many exocrine organs, the secretory end pieces and the ducts are partly covered by cells with long processes that form an interlacing network. These cells resemble smooth muscle cells in several important aspects, yet clearly are epithelial cells, and thus are referred to as myoepithelial cells (MEC) [1]. The MEC were first discovered in the breast tissue by Krause in 1865. Since then it has been observed in the terminal end pieces and ducts of most of the exocrine glands such as salivary, mammary, sweat, lacrimal and bronchial glands. The description of these cells is diverse. Various authors have described them as “spindle shaped cells”, “star shaped cells” or “basket cells” until the term “myoepithelial cells” was conferred to it. Most of the authors have studied this cell in detail in the mammary glands only until it was Tamarin in 1966 that provided a vivid image of a typical acinus-associated MEC in the salivary gland. He typically described the appearance of the cell on the acinar unit as being “like an octopus sitting on a rock”. These cells lie between the basal lamina of the acinar and ductal cells at the terminal portion of the salivary glands [1,2].

Positive identification of salivary gland MEC on routine microscopic preparations is very difficult. Fortunately modern sophisticated microscopic techniques have resulted in a surge of new information on this cell such as exposure of MEC by chemical removal of periacinar connective tissue and basement membrane deposits [2]. MEC have many cytoplasmic processes which embrace glandular cells. Their nuclei are localized in the cell body. Most of the cytoplasmic organelles are found in the small areas around the nucleus. The remainder of the cytoplasm is filled with filaments and vesicles which are morphologically similar to those found in smooth muscle cells [3].

After studying the structure of MEC in detail researchers focussed on identifying the physiological functions of these cells. The function of MEC was identified by an essential term in biologic kinetics (kinesiology) which states “form defines the function”. The shape of the MEC suggested that its contraction might reduce the luminal volume in glandular endpieces, and these cells may play a role in expelling secretory products from glandular endpieces to the excretory duct system which was later proved experimentally. Thus one of the chief functions of MEC was determined [4]. Association of tumours with MEC was determined when scientists found that a variety of tumours occurred in salivary glands and breast as compared to pancreas and concluded that this was because of presence of MEC in the former two glands [5,6] [Table/Fig-1].

S. No.	Year	Study Done	Author
1	1865	Identification of MEC in breast tissue	Krause
2	1966	MEC studied for the first time in a salivary gland	Tamarin
3	1971	Study of role of MEC in salivary gland tumours	Hubner et al.,
4	1973	Role of MEC in expulsion of saliva determined	Emmelin et al.,
5	1974	Fluoroscent property of MEC identified	Puchtler et al.,
5	1976	Cytochemical analysis of MEC in a salivary gland	Han et al.,
6	1977	Role of MEC in histogenesis of salivary gland tumours	Regezi et al.,
7	1985	IHC antibodies against normal MEC identified	Dairkee et al.,
8	1986	Silver staining of MEC identified	Linzell
9	1986	Special stains for MEC identified	Kellogg et al.,
10	1994	Identification of actin as marker for NMEC	Araujo et al.,
11	1997	Identification of myosin as marker for NMEC	Savera et al.,
12	1999	Identification of calponin as marker for NMEC	Prasad et al.,
13	2004	Identification of maspin as marker for NMEC	Rde et al.,
14	2011	Identification of WT1 as marker for NMEC	Langman et al.,
15	2013	Identification of role of EWSR1 in myoepithelial cell tumours	Shah et al.,

[Table/Fig-1]: Review of myoepithelial cells in health and in tumours

This review aims to describes the MEC in detail regarding its development, distribution, and function mainly in the salivary glands. It also emphasises its role in the development of various tumours arsing from these glands and methods to identify this particular cell in physiology as well as in pathology.

Distribution and Ultrastructure

The MEC in the salivary glands are stellate or spiderlike, with a flattened nucleus scanty, perinuclear cytoplasm and long branching processes that embrace the secretory and duct cells. The configuration of MEC depends on its location. Those associated with acinus are multipolar. They consist of a central body and four to eight processes radiating from it. Each process subdivides to give rise to second and even third generation of branches. Thus the net effect is that the acinus is embraced by many processes of the MEC [1]. In the intercalated ducts the MEC have a more fusiform shape and are elongated with few short processes. The processes in the acini lie in 'gutters', hence the outline of the acini appears smooth but in the intercalated duct, the processes runs longitudinally on the surface creating a bulge [7].

Ultrastructurally, the MEC consists of two moieties, a filamentous, and a non-filamentous one. The filaments are arranged parallel and aggregated as bundle and are approximately 4 nm in diameter, resembling the myofilaments of smooth muscle. The non-filamentous portion of the MEC contains the nucleus and the organelles. The nucleus is usually flattened in the plane parallel to the basement membrane, and may be scalloped in outline. The Golgi apparatus and prominent centrioles are also situated close to the nucleus. Mitochondria are not abundant, and they are evenly distributed in the perikaryon and in the cell processes. The endoplasmic reticulum consists of a few small cisternae [7].

FUNCTIONS OF MEC

Numerous functions of the MEC have been elucidated in the literature which include contraction, propagation of neural stimuli, basement membrane production, transport of metabolites and a role in tumour suppression [1,8].

Contraction

Since their discovery, the principle role of MEC that has been considered is its ability to contract. It was found that MEC played a very minor role in the expulsion of saliva during a normal basal flow but played an important role when secretion was required at faster rates such as during stimulation [9].

Propagation of Neural Stimuli

Though not proved, propagation of nerve stimuli is considered one of the functions of MEC. The detection of cholinesterase cyto-chemically and the presence of gap junctions ultramicroscopically support the hypothesis that MEC have a role in propagation of neural stimuli [1].

Basement Membrane Production

MEC plays an important role not only in the production of proteins such as fibronectin, laminin and elastin in the basement membrane but also acts as an scaffold for the multiplication and differentiation of these proteins [2].

Transportation of Metabolites

This is a controversial function that has been attributed to the MEC. The facts supporting this are that the presence of basal infoldings, presence pinocytotic vesicles, positive staining for and an increased alkaline phosphatase and magnesium dependant adenosine triphosphatase (ATPase) activity. However, it should be noted that ATPase activity in MEC can also be due the fact that its is a contractile cell [1,2].

Role in Tumour Suppression

MEC appears to resist neoplastic transformation. It has been shown that in the neoplastic state, these cells have a lower proliferation than basal type epithelial cells and secretes substances that inhibit tissue angiogenesis, invasion and metastasis [10,11].

IDENTIFICATION OF MEC

This is one of the most important aspects of MEC to be known because over the years lot of controversy has been around for histological identification of MEC. This section describes the various techniques that can be employed to identify these cells in the normal salivary gland.

With hematoxylin and eosin staining, the myoepithelial cell appears to be small and fusiform, its long axis being parallel to the basement membrane. It takes up a much darker stain than the ductal epithelium [12]. The various special stains used to identify MEC and the stains that demonstrate the property of birefringerence and fluroscence of myosin and actin filaments has been described in [Table/Fig-2] [13-15]. The introduction of immunohistochemistry (IHC) to pathologists saw a new era in identification of both MEC and neoplastic MEC (NMEC). The various markers that have been used to identify these cells have been tabulated in [Table/Fig-2] [16].

MEC IN SALIVARY GLAND PATHOLOGY

The role of MEC in salivary gland tumours is well established. It can be said that MEC has the capacity to differentiate into epithelial as well as the mesenchymal components in a tumour and these tumour cells have been termed the NMEC. The ability of NMEC to provide a mesenchymal component to salivary gland tumours can be due to fact that MEC exhibits features of smooth muscle [2]. Eversole and later, Regezi and Batsakis were the ones who helped to understand the importance of NMEC in salivary gland tumours in the bicellular theory. It has to be understood that the NMEC has the ability to provide a wide spectrum of cytological and extracellular matrix (ECM) differentiation. It can also produce different architectural patterns in a tumour. The variety of morphologies that a NMEC can differentiate into is,

1. Angulate/basaloid: These cells are small with a hyperchromatic nuclei and a faint eosinophilic cytoplasm.
2. Epitheloid cells: These cells are polygonal with a vesicular nuclei and ample cytoplasm.
3. Clear cells: These cells appear clear due to glycogen in their cytoplasm.
4. Spindle cells: These cells are elongated, fusiform with pale cytoplasm.
5. Plasmacytoid (hyaline cells): These cells have a bright eosinophilic cytoplasm with eccentric nucleus.

The varieties of ECM that can be produced by NMEC include myxoid, chondroid, myxochondroid, and fibrous, elastic and even osteoid type of ECM. Similarly, the variety of architectural patterns that NMEC can produce are

1. Myxoid pattern: due to production of abundant chndromyxoid matrix, the tumour cells are loosely and randomly distributed.
2. Solid (non-myxoid) pattern: Cells are arranged in the form of nests, sheets intervened by a hyalinized matrix.
3. Reticular pattern : Seen as an anastomozing pattern containing epitheloid-myoepithelial cells.
4. Microcystic/Pseudocystic pattern: Presence of varied sizes of loose cystic spaces formed by accumulation myxoid matrix within the nests of tumour cells.
5. Cribriform/pseudoglandular pattern in which clusters of epi-theloid cell form cribriform structures and pseudolumen due to their myxoid matrix production [17].

NEOPLASMS WITH MEC DIFFERENTIATION [TABLE/FIG-3]

Recently Nagao et al., have classified the tumours with and without MEC cell differentiation. According to them the benign tumours that exhibit MEC cell differentiation are pleomorphic adenoma, myoepithelioma and basal cell adenoma. They did not include

sebaceous adenoma and oncocytoma which were considered to contain a MEC component earlier [18]. Though, it has not been determined whether the MEC observed in the tumour tissue carries itself tumourigenic potential or functions as a supporter of tumour induction, understanding its differentiation is very important to elucidate the pathogenesis of various salivary gland tumours [19]. It has to be noted that the variety of cytological, ECM and architectural patterns produced by NMEC can occur alone or along with other tumour components and according to this, the lesions showing NMEC differentiation can be classified under two headings:

i. Tumours with complete/predominant NMEC participation (benign and malignant).

ii. Tumours with partial NMEC participation (benign and malignant).

Tumours with Complete/Predominant NMEC Participation (BENIGN)

Pleomorphic Adenoma and Myoepithelioma: Tumour cells seen in pleomorphic adenoma and myoepithelioma are termed NMEC and are polygonal, spindle, or plasma cell-like in shape, which they are arranged as sheet-, clump-, or strand-structure, and are admixed with myxoid, chondroid or osseous components which as mentioned before produced by the NMEC which attain these properties by way of differentiation into mesenchymal type of cells [20,21].

S. No.	Identification Methods	Markers or stains used
1	Special stains	Silver staining, tannic phosphomolybdic acid-dye [21,22]
2	Birefringence	Thiazine Red R, Levanol Brilliant Red BB
3	Fluorescence	Rhodamine-phalloidin, Nitrobenzoxadiazole-phalacidin
4	Enzyme Histochemistry	Alkaline phosphatise, Adenosine triphosphatase, Glycogen phosphorylase, Inosine diphosphatase
5	Immunohistochemistry	α-SMA, SMMHC, h-caldesmon, Basic calponin, CK14, CK5, CK17, α1β1 integrin, Metallothionein, p63, CD29 and CD109.

[Table/Fig-2]: Identification of MEC in salivary glands

Benign Tumours	With Partial NMEC participation	Basal cell adenoma
	With complete/predominant NMEC participation	Pleomorphic adenoma Myoepithelioma
Malignant Tumours	With Partial NMEC participation	Basal cell adenocarcinoma Polymorphous low grade carcinoma (very few cases)
	With complete/predominant NMEC participation	Malignant myoepilioma Adenod cystic carcinoma Epithelial- Myoepithelial carcinoma Metastasizing pleomorphic adenoma Carcinoma ex pleomorphic adenoma

[Table/Fig-3]: Tumours showing NMEC differentiation

Tumours with Partial NMEC Participation (BENIGN)

Basal cell adenoma: The involvement of MEC in the pathogenesis of this tumour has been very controversial as almost all the histological and electron microscopic studies have not revealed the presence of NMEC in these benign tumour. However, few studies done using IHC have revealed presence of the NMEC in these tumours and their location has been correlated with that of a normal MEC in the duct [22-24].

Tumours with Complete/Predominant NMEC Participation (MALIGNANT)

Malignant myoepithelioma: The range of cell types seen in benign myoepitheliomas includes epithelioid cells (the most frequent) often arranged in trabeculae or pseudo-acinar structures with cleft-like spaces (sometimes appearing signet ring-like), vacuolated (sometimes lipoblast like), hyaline (plasmacytoid) and spindle to stellate. In most malignant myoepitheliomas one cell type predominates, but there is usually a minority component of other cell types. The nuclei of malignant myoepitheliomas may be relatively uniform, small to intermediate sized and composed of finely distributed chromatin, lacking obvious nucleoli, or there may be marked cytological atypia, with enlarged pleomorphic nuclei, showing chromatin clumping and large nucleoli [22].

Epithelial-Myoepithelial carcinoma: The tumour has a distinctive histopathologic pattern with a proliferation of ductular structures. The inner cells of these ductules constitute the epithelial component whereas outer cell layer that surrounds the ductules is considered the clear cell myoepithelial component of EMEC [25].

Adenoid cystic carcinoma: A malignant tumour, in which the occurrence of MEC has been much disputed, is the adenoid-cystic carcinoma or cylindroma. Adenoid cystic carcinoma especially the cribriform variant is composed of epithelial and abluminal cells, the latter usually being much more abundant. Although the histological appearance is much more basaloid than myoepithelial, a proportion of the abluminal cells show ultrastructural and immunohistochemical evidence of myoepithelial differentiation. Also, the hyaline material seen is a result of the production by NMEC [6,26].

Metastasizing pleomorphic adenoma and Carcinoma ex pleomorphic adenoma: Metastasizing pleomorphic adenomas are a small percentage of pleomorphic adenomas that have obvious malignant components in epithelial or in both epithelial and mesenchymal components that can metastasize. The presence of NMEC dominates in this tumour and also in carcinoma ex pleomorphic adenoma as suggested both histologically and immunohistochemically [22].

Tumours with Partial NMEC Participation (MALIGNANT)

Basal cell adenocarcinoma: It is a rare tumour which is differentiated from its benign counterpart from its ability to invade adjacent structures brought about by the NMEC component [27].

Polymorphous low grade adenocarcinoma: Few authors have found that expression of some immunohistochemical markers of NMEC has been seen in very few cases of PLGA thus speculating the participation of these cells in this malignant tumour [28].

Markers for Identification of Neoplastic MEC

Salivary gland tumours are characterized by a wide variety of histological types, which makes their classification and diagnosis difficult. This complexity has been attributed to the NMEC. However, it has not yet been established that they actually originate from MEC because they often lack epithelial and smooth muscle proteins that are normally expressed by MEC [29,30]. Identification of the NMEC cannot be achieved without knowing which proteins are expressed by developing, immature MECs. It is therefore important to determine what proteins might be specifically expressed - and those which are not expressed by the MEC so that an immunohcytochemical profile of these cells can be established [2]. Also, identification of proteins expressed by these cells can be helpful in identifying the origin and also help in understanding the biology of the tumour [29].

The NMEC express numerous proteins as expressed by the MEC. They are α-SMA, SMMHC, CK14, p63 and calponin [31-40]. Apart from these proteins there are few proteins that have identified to identify NMEC. Vimentin that is not expressed by MEC is considered to be a very sensitive marker for NMEC. The reason that has been stated it is expressed in basal cell adenoma, ACC and in PLGA, but did not find its expression in tumours arising from the ducts or Warthin's tumour, inverted ductal papilloma or mucoepidermoid

carcinoma. Hence, it has been theorised that vimentin is seen as one of the earliest differentiation markers for NMEC [35].

S100 protein, named as it is soluble in a saturated ammonium sulphate solution has also been useful to the label NMEC [39]. Its expression in MEC in normal salivary glands and NMEC in various salivary gland tumours has produced variable results. The NMEC in pleomorphic adenomas showed positivity but this discrepancy was attributed to the fact that there is a rich autonomic nerve supply to the acini and ducts. Hence it is not presently considered to be reliable markers for NMEC. Similar to S100 protein, glial fibrillary acidic protein (GFAP) has shown positivity in the ductal cells of the salivary glands rather than the MEC. But its expression in the NMEC in pleomorphic adenoma has shed new light in understanding the development of such tumours and can be asserted that these neoplastic cells are at a very early stage of differentiation and this marker has been used to differentiate between basal and NMEC along with S100, actin and calponin [41].

Maspin has been considered a reliable marker for NMEC of the breast, but its expression in salivary gland tumours has been very limited. But it has been used as a prognostic marker. As we have already discussed, MEC plays a role in tumour suppression. Few authors have studied its expression in salivary gland tumours and correlated with tumour invasion and have theorised that maspin might be an important prognostic marker as its expression is high in tumours that show minimal invasion [42,43]. Also, recently WT1 has shown to be a promising marker for NMEC as its expression in pleomorphic adenoma seems to correlate with the NMEC [44].

RECENT ADVANCES

Recently researchers have sought the relation between tumours of MEC arising from salivary glands (major and minor) and some of the MEC tumours arising in the soft tissues such as benign mixed tumour in the skin and myoepithelial tumour/parachordoma in the soft tissue. These soft tissues lesions have been found to have genetic aberrations in the PLAG 1 (Pleomorphic adenoma gene 1), which is common alteration in pleomorphic adenoma and EWSR1 gene (Ewing sarcoma breakpoint region 1). Though alterations PLAG1 have been observed in myoepitheliomas of the salivary glands, intital reports have not shown any alteration on EWSR1 gene. Though intial reports suggest that myoepithelial tumours are a separate entity and cannot be included in subset of tumours arising from its soft tissue counterparts, further research in this direction with large sample size is required to say anything conclusively [45-49].

CONCLUSION

Numerous functions of MEC have been elucidated but the most important role as far as pathologists are concerned is its ability to suppress tumour formation and hence acts as a prognostic marker. These cells have been studied under varied conditions and various stains but still a proper IHC marker for either the normal or NMEC has not been found. Also the fact that these cells have complex make-up, the NMEC has the ability to take any of several very different morphological forms, and another important aspect regarding the MEC is that it plays a significant role in tumour pathogenesis and understanding this cell in detail is required to comprehend the pathogenesis of numerous salivary gland tumours. Hence, proper research and techniques has to be applied to obtain significant knowledge regarding MEC and its role in salivary gland tumours.

REFERENCES

[1] Redman RS. Myoepithelium of Salivary Glands. *Microscopy Research and Technique.* 1994;27:25-45.

[2] Raubenheimer EJ, van Niekerek JP, Hauman CHJ. Salivary myoepithelium: distribution, structure, functions and pathologic proliferations. *Journal of the DASA.* 1987;42:631-37.

[3] Lemullois M, Rossignol B, Mauduit P. Immunolocalization of myoepithelial cells in isolated acini of rat exorbital lacrimal gland: Cellular distribution of muscarinic receptors. *Bid Cell.* 1996;86:175-81.

[4] Satoh Y, Oomori Y, Ishikawa K, Ono K. Configuration of myoepithelial cells in various exocrine glands of guinea pigs. *Anat Embryol.* 1994;189:227-36.

[5] Sopel M. The myoepithelial cell: its role in normal mammary glands and breast cancer. *Folia Morphol.* 2010;69:1–14.

[6] Hubner G, Kleinsassera JK, Schiefer G. Role of myoepithelial cells in the development of salivary gland tumours. *Cancer.* 1971;21:1255-61.

[7] Tandler B. Ultrastructure of the human submaxillary gland, iii. Myoepithelium. *Zeitschrift ffir zellforschung.* 1965;68:852-63.

[8] Caselitz J, Walther B, Wustrow J, Seifert G, Weber K, Osborn M. A monoclonal antibody that detects myoepithelial cells in exocrine glands, basal cells in other epithelia and basal and suprabasal cells in certain hyperplastic tissues. *Virchows Arch.* 1986;409:725-38.

[9] Emmelin N, Gjorstrup P. On the function of myoepithelial cells in salivary glands. *J Physiol.* 1973;230:185-98.

[10] Zarbo RJ. Salivary Gland Neoplasia: A Review for the Practicing Pathologist. *Modern Pathology.* 2002;15:298-323.

[11] Deugnier MA, Teulière JA, Faraldo MF, Thiery JP, Glukhova MA. The importance of being a myoepithelial cell. *Breast Cancer Res.* 2002;4:224-30.

[12] Sarkar K, Kallenbach E. Myoepithelial cells in carcinoma of human breast. Myoepithelial cells in carcinoma of human breast. *Am J Path.* 1966;49:301-07.

[13] Linzell JZ. The silver staining of myoepithelial cells, particularly in the mammary gland, and their relation to the ejection of milk. *Journal of Anatomy.* 1952; 86;49-57.

[14] Kellogg A, McAljliffe WG, Schrodt GR. A Modification of the Tannic Acid Phosphomolybdic Acid-Dye Stain for Demonstrating Myoepithelial Cells in Formalin Fixed Tissue. *Biotechnique & Histochemistry.* 1986;61:219-25.

[15] Puchtler H, Waldrop FW, Carter MG, Valentine LG. Investigation of Staining, Polarization and Fluorescence Microscopic Properties of Myoepithelial Cells. *Histochemistry.* 1974;40:281-89.

[16] Ianez RF, Buim ME, Coutinho-Camillo CM, Schultz R, Soares FA, Lourenco SV. Human salivary gland morphogenesis: myoepithelial cell maturation assessed by immunohistochemical markers. *Histopathology.* 2010;57:410–17.

[17] Redder CP, Kandagal VS, Vibhute N, Ingaleshwar PS, Shetty SJ, Ahamad S. Myoepithelial cells: Current perspectives in salivary gland tumours. *Clin Cancer Investig J.* 2013;2:101-05.

[18] Nagao T, Sato E, Inoue R, Oshiro H, Takahashi RH, Nagai T, et al. Immunohistochemical Analysis of Salivary Gland Tumours: Application for Surgical Pathology Practice. *Acta Histochem. Cytochem.* 2012;45: 269–82.

[19] Shirasijna K, Sato M, Miyazaki T. A Myoepithelial Cell Line Established from a Human Pleomorphic Adenoma Arising in Minor Salivary Gland. *Cancer.* 1980;45:297-305.

[20] Ellis GL, Auclair PL, Gnepp DR. Surgical pathology of the salivary glands.Volume 25.

[21] Takeda Y, Shimono M. Pleomorphic adenoma with nuclear pausading arrangement of modified myoepithelial cells: histopathologic and immunohistochemical study. *Bull Tokyo dent Coll.* 1999;40:27-34.

[22] Simpson RHW. Myoepithelial tumours of the salivary glands. *Current Diagnostic Pathology.* 2002;8:328-37.

[23] 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;124:401–05.

[24] Yu GY, Ussmueller J, Donath K. Histogenesis and development of membranous basal cell adenoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86:446-55.

[25] Alves PM, Silva AC, Godoy GP, Queiroga DGC, Queiroz LLMG, Galvão H. Unusual epithelial-myoepithelial carcinoma in palate- case report and immunohistochemical study. *J Clin Exp Dent.* 2010;2:22-25.

[26] Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer.* 1984;54:1062–69.

[27] Jung MJ, Roh JL, Choi SH, Nam SY, Kim SY, Lee SW, et al. Basal cell adenocarcinoma of the salivary gland: a morphological and immunohistochemical comparison with basal cell adenoma with and without capsular invasion. *Diagnostic Pathology.* 2013;8:171.

[28] Prasad ML, Barbacioru CC, Rawal YB, Husein O, Wen P. Hierarchical cluster analysis of myoepithelial/basal cell markers in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. *Mod Pathol*. 2008;21:105-14.

[29] Dardick I, Burford-Mason. Current status of histogenetic and morphogenetic concepts of salivary gland tumourigenesis. *Crit Rev oral Biol Med.* 1993;4,639-77.

[30] Ogawa Y, Toyosawa S, Ishida T, Ijuhin N. Keratin 14 immunoreactive cells in pleomorphic adenomas and adenoid cystic carcinomas of salivary glands. *Virchows Arch.* 2000;437:58-68.

[31] Araujo VC, Carvalho YR, Araujo NS. Actin versus vimentin in myoepithelial cells of salivary gland tumours. *Oral Surg Oral Med Oral Pathol.* 1994;77:387-91.

[32] Scarpellini F, Marucci G, Foschini MP. Myoepithelial differentiation markers in salivary gland neoplasia. *Pathologica*. 2001;93:662-67.

[33] Savera AT, Gown AM, Zarbo RJ. Immunolocalization of three novel smooth muscle-specific proteins in salivary gland pleomorphic adenoma: assessment of the morphogenetic role of myoepithelium. *Mod Pathol*. 1997;10:1093-100.

[34] Prasad AR, Savera AT, Gown AM, Zarbo RJ. The myoepithelial immunophenotype in 135 benign and malignant salivary gland tumours others than pleomorphic adenoma. *Arch Pathol Lab Med.* 1999;123:801-06.

[35] Furuse C, Suzana O, de Sousa M, Nunes FD, de Magalhaes MHCG, de Araujo VC. Myoepithelial Cell Markers in Salivary Gland Neoplasms. *International Journal of Surgical Pathology.* 2005;13:57-65.

[36] Foschini MP, Scarpellini F, Gown AM, Eusebi V. Differential expression of myoepithelial markers in salivary, sweat and mammary glands. *Int J SurgPathol.* 2000;8:29-37.
[37] Dairkee SH, Blayney C, Smith HS, Hackett AJ. Monoclonal antibody that defines human myoepithelium. *Proc Natl Acad Sci.* 1985;82:7409-13.
[38] Edwards PC, Bhuiya T, Kelsch RD. Assessment of p63 expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and basal cell and canalicular adenomas. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2004;97:613-19.
[39] Leong ASY, Cooper K, Leong FJWM. Manual of Diagnostic Antibodies for Immunohistology; Greenwich Medical Media Limited;1999.
[40] Deihemy P, Mazhooni P, Torabina N. Study of Myoepithelial Cell Markers in Pleomorphic Adenoma and Mucoepidermoid Carcinoma of Salivary Glands. *Dental Research Journal.* 2006;3:1-9.
[41] Okura M, Hiranuma T, Tominaga G, Yoshioka H, Aikawa, Shirasuna K, et al. Expression of S-100 Protein and Glial Fibrillary Acidic Protein in Cultured Submandibular Gland Epithelial Cells and Salivary Gland Tissues Histogenetic Implication for Salivary Gland Tumours. *American Journal of Pathology.* 1996;148:54-59.
[42] Rde NL, Martins MT, de Araújo VC. Maspin expression in normal and neoplastic salivary gland. *J Oral Pathol Med*. 2004;33:435-40.
[43] Martins MT, Altemani A, Freitas L, de Araujo VC. Maspin expression in carcinoma ex pleomorphic adenoma. *J Clin Pathol.* 2005;58:1311–14.
[44] Langman G, Andrews CL, Weissferdt A. WT1 expression in salivary gland pleomorphic adenomas: a reliable marker of the neoplastic myoepithelium. *Mod Pathol*. 2011;24:168-74.
[45] Romeo S, Tos APD. Soft tissue tumours associated with EWSR1 translocation. *Virchows Arch.* 2010;456:219–34.
[46] Antonescu CR, Zhang L, Chang NE, Pawel BR, Travis W, Katabi N, et al. EWSR1-POU5F1 fusion in soft tissue myoepithelial tumours. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. *Genes Chromosomes Cancer.* 2010;49:1114-24.
[47] Shah AA, LeGallo RD, van Zante A, Frierson HF Jr, Mills SE, Berean KW, et al. EWSR1 genetic rearrangements in salivary gland tumours: a specific and very common feature of hyalinizing clear cell carcinoma. *Am J Surg Pathol*. 2013;37:571-78.
[48] Matsuyama A, Hisaoka M, Nagao Y, Hashimoto H. Aberrant PLAG1 expression in pleomorphic adenomas of the salivary gland: a molecular genetic and immunohistochemical study. *Virchows Arch*. 2011;458:583-92.
[49] Antonescu CR, Zhang L, Shao SY, Mosquera JM, Weinreb I, Katabi N, et al. Frequent PLAG1 gene rearrangements in skin and soft tissue myoepithelioma with ductal differentiation. *Genes Chromosomes Cancer*. 2013;52:675-82.

PARTICULARS OF CONTRIBUTORS:
1. Senior Lecturer, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India.
2. Professor, Department of Oral Pathology, Rajah Muthiah Dental College and Hospital, Annamalai Nagar, Tamil Nadu, India.
3. Professor and HOD, Department of Oral Pathology, Rajah Muthiah Dental College and Hospital, Annamalai Nagar, Tamil Nadu, India.
4. Professor and HOD, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur, Andhra Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Ravi Teja Chitturi,
Senior Lecturer, Department of Oral Pathology, SIBAR Institute of Dental Sciences, Guntur 522509, Andhra Pradesh, India.
E-mail: dr.raviteja@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 22, 2014**
Date of Peer Review: **Jan 07, 2015**
Date of Acceptance: **Feb 08, 2015**
Date of Publishing: **Mar 01, 2015**