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Review Article

Histogenesis of salivary gland neoplasms

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ABSTRACT:
Salivary gland tumours offer a mydriad of diversity thus maintaining the ambiguity of these neoplasms. Still the enigma of diagnosing these salivary gland tumours incurs as a challenge in routine practice especially in the realm of a pathologist. It is important for the pathologist to access the cytoarchitectural features and profile of these neoplasms and correlate them with histiogenetic concepts. Insight into the underlying histogenic, morphogenic, and genetic pathways responsible for various salivary gland neoplasms have resulted in improved diagnostic tools and thereby more competent therapeutic modalities. Latest developments in the field of immunohistochemistry, genetic alterations and molecular biology have helped us better in defining and diagnosing such lesions. The present article is aimed at reviewing and summarizing the historical perspective as well as the current concepts regarding the histogenesis of salivary gland tumours and correlating this with their molecular profiles; thereby highlighting their relevance to routine diagnosis. Emphasis has also been laid upon few common benign and malignant salivary gland neoplasms in understanding and deciphering the origin and histogenesis of these tumours.
Key words: Histogenesis, salivary gland neoplasms, salivary gland tumours

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INTRODUCTION

Tumours of salivary glands constitute a diverse group of lesions of great morphologic variation and remain a diagnostic dilemma due to their complex behavior. This complexity is attributed to heterogeneity of the cells of origin of these lesions. The problem is exacerbated by the ability of these cells to differentiate and alter into various morphological subtypes ensuing a multitude of histomorphological patterns. Progression of salivary gland tumours can take the form of malignant transformation of a benign tumour, progression from low-grade to high-grade carcinoma, dedifferentiation, or stromal invasion of an in situ carcinoma.[1] This also leads to a recurrent overlap of microscopic features among various neoplasms and sometimes even between benign and malignant lesions causing significant diagnostic predicament which sometimes may even not be resolved by immunohistochemical analysis. Advances in molecular pathology have uncovered genetic patterns and oncogenes by immunohistochemistry, fluorescent in situ hybridization, and next–generation sequencing, that may potentially contribute to innovating diagnostic approaches in identifying various salivary glands neoplasms (SGN).[2]The morphology of salivary gland tumours reflect the cellular make up of basic ductoacinar unit of normal salivary gland.[3]Use of immunohistochemistry to differentiate between luminal and abluminal cells can help in understanding the complex architecture of salivary gland tumours and aid in its diagnosis.[1] Insight into the underlying histogenic, morphogenic, and genetic pathways responsible for various SGN have resulted in improved diagnostic tools and thereby more competent therapeutic modalities.[2]Although the genetic makeup of each tumour type appears to be unique, there are common pathways and themes shared among the various types of salivary gland tumours—abnormalities in epigenetic regulation, oncogenic fusion products, and overexpression of cell surface receptors. Therefore the advent and the now widespread use of new genetic methods have paved the way for promising advancements in our understanding of the molecular biology underlying each type of tumour.[4]The present article is aimed at reviewing and summarizing the historical perspective as well as the current concepts regarding the

histogenesis of salivary gland tumours and correlating this with their molecular profiles; thereby highlighting their relevance to routine diagnosis. Emphasis has also been laid upon few common benign and malignant salivary gland neoplasms in understanding and deciphering the origin and histogenesis of these tumours.

Salivary gland development is an example of branching morphogenesis, a process fundamental to many developing organs, including lung, mammary glands, pancreas, and kidney. All salivary glands develop as the initial thickening of the epithelium of the stomodeum. Although, it is not yet clear, the parotid gland is believed to develop from oral ectoderm, whereas the submandibular and sublingual glands are believed to develop from endodermal germ layers.[5]

SALIVARY GLAND NEOPLASMS

A. HISTOGENETIC CONCEPTS

Earlier concepts of pathogenesis of SGN concentrated on the histologic cell of origin. The adult salivary glands are composed of reserve cells that are postulated to replicate pathologically to form SGN. The four commonly hypothesized histogenetic theories are-

- Basal reserve cell or progenitor cell theory: According to this basal cell of the excretory and intercalated ducts function as reserve cells for more highly differentiated components of the functional salivary complex. [3,6]
- Pluripotent unicellular reserve cell theory: Stated that the basal cells of excretory ducts were responsible for the development of all salivary gland units [3,6]
- Semi-pluripotent bicellular reserve cell theory: A more plausible interpretation of the reserve cell theory suggested that the basal cells of the excretory duct (excretory duct reserve cells) produced squamous or mucin-producing columnar cells, and those from the intercalated ducts (intercalated duct reserve cells) were responsible for development of intercalated, striated, and acinar elements [3,6,7]
- Multicellular theory: Further investigation provided evidence that all mature cell types, including acinar and basal cells in salivary gland tissue were capable of proliferation. This theory presumes that SGN originated from the differentiated or adult cell counterpart from within the functional salivary ducto-acinar complex.[3,6]

B. MORPHOGENETIC CONCEPT

The salivary glands are composed of luminal (acinar and ductal) and abluminal (myoepithelial and basal) cells. These act as prospective subjects for neoplastic change as they swiftly enter the cell cycle. Batsaki has been instrumental in emphasizing the bicellular constitution (luminal and neoplastically modified myoepithelial cells) of certain salivary gland tumours; these include pleomorphic adenoma, Adenoid cystic carcinoma (AdCC), epithelial myoepithelial carcinoma, and terminal duct carcinoma. This feature has been extended to additional types of salivary gland tumours, such as certain monomorphic adenomas and Acinic cell carcinoma (ACC), mucoepidermoid carcinomas, malignant mixed tumour and Warthin's tumour. In salivary gland tumours, the myoepithelial cell component rarely has structural features approaching those of the normal cell. This even applies to myoepitheliomas in which there is a range of structural modifications resulting in a variety of cell form such as spindle, plasmacytoid, epithelial, and clear. [5]Dardick deemed cellular morphology and cellular differentiation, derived from differential gene expression of a stem cell, in conjunction with tumour extra cellular matrix production, to be better predictors of SGN, when compared to a specific proposed cell of origin. [8]

PLEOMORPHIC ADENOMA

Pleomorphic adenomas (PA) are benign salivary gland tumours, also known as benign mixed tumour, is the most common salivary gland tumour. The “pleomorphic” nature of the tumour can be described on the basis of its dual origin i.e. epithelial and myoepithelial components. Various histogenetic pathways postulating the origin of PA have been described. A neoplastically altered acinar or ductal cell, with the potential for expressing myoepithelial cell features, could be involved in the genesis of salivary gland pleomorphic adenomas.[8]Other findings indicate that benign pleomorphic adenomas of the major salivary glands are pure epithelial cell tumours. The histologic complexity of these neoplasms is due to the ability of the neoplastic ductular myoepithelial cell to modulate its morphologic appearance and intermediate filament composition, and to produce large amounts of matrix substances postulating that these tumours arise from neoplastically transformed intercalated ducts.[9]The neoplastic myoepithelial cells in the myxoid region probably derive from the periphery of the double-layer ductal structure, they secrete the proteoglycans forming the myxoid region and play an important role in the histogenesis of PA.[10]There are several translocations that have been identified for PA. Genetic aberrations occur involving the transcription factor genes PLAG1 and HMGA2. PLAG1 is a proto–oncogene located on chromosome 8q12.[11]Overexpression leads to the activation of various signaling pathways, including WNT or HRAS, which determine the fate of cells. HMGA2 is located on chromosome 12q14 and is the second most common genetic event occurring in PA. Though unclear, the molecular mechanism for its overexpression is likely to encode for an architectural transcriptional factor that binds to the adenosine–

thymine DNA sequences, thus acting as transcription regulators for cell death, growth, and proliferation.[12]Since PLAG1 or HMGA2 gene translocations are exclusive to PA, its diagnosis using aids like IHC, RT-PCR and FISH are of great significance. Positive immunoexpression of PLAG1 and GFAP in this tumour has been helpful in its affirmative diagnosis.[13]

CARCINOMA ex PLEOMORPHIC ADENOMA

Carcinoma ex Pleomorphic Adenoma (CPA) is a tumour that develops due to malignant transformation of PA. Carcinoma ex pleomorphic adenoma is a rare, aggressive, poorly understood malignancy, which usually occurs in the salivary glands and accounts for most reported cases of malignant mixed tumours. In CPA, an epithelial malignancy develops in association with a primary or recurrent benign pleomorphic adenoma.[14,15]Carcinoma areas characterized by ductal structures containing both benign myoepithelial cells positive for alpha-smooth muscle actin (alpha-SMA), vimentin and CK 14 and proliferating atypical luminal cells reactive for CK7, CK8 and CK 19. Tumours with a myoepithelial component were composed mainly or exclusively of cells that expressed vimentin and alpha-SMA.[16]The expression of PLAG1 and HMGA2 is common for both PA and CPA. [12]There is evidence that CPA could be differentiated by over expression of TP53, AR, and HER2 genes.[2] It has been found that, irrespective of the fact that there is varied appearance in its histology, CPA exhibits the same PLAG1 and HMGA2 rearrangements. In addition, ERBB2 over expression and amplification similar to those which occur in SDC [17,18,19] , copy number gains involving 9p23-p22.3 (NFIB) and 22q12-qter (PDGFB) [20], MDM2 amplification [21,22], loss of heterozygosity, and microsatellite alterations in the p53 and RB genes and at chromosomal location 5q [23] are all secondary genetic alterations detected in CPA and may be of importance for disease progression from PA.

BASAL CELL ADENOMA

Basal Cell adenoma is an infrequently occurring benign neoplasm characterized by a uniform phenotypic distribution of basaloid epithelium arranged in a rigid, trabecular, tubular, or membranous pattern, reported as a definite entity in 1967 by Kleinsasser and Klein. The basaloid cells can take on two or more morphological forms. One of the morphologic forms is a small cell having scanty cytoplasm, with round nucleus and deeply basophilic nucleoli arranged in palisading shapes. The other type is described as a large cell having an amphophilic to eosinophilic nucleus that is more ovoid and paler staining. Arujo, et al. observed that luminal ductal cells from the basal cell adenomas, express CK 7, 8, 14, and 19 while the non-luminal cells were rarely positive to CK 14. On the outside of the solid cell nests, there were smaller elongated myoepithelial-like cells, which expressed cytokeratin 14 and vimentin. A peri-cytoplasmic rim pattern of CEA immunostaining from ductal structures of basal cell adenomas is similar to that expressed by luminal columnar cells from striated ducts of normal salivary glands. A positive reaction to vimentin in both epithelial and stromal components in basal cell adenomas has been observed.[16,24] The genetic alterations in Basal cell Adenoma are CYLD LOH and CTTNB1 mutations.[25]

BASAL CELL ADENOCARCINOMA

Basal cell adenocarcinoma is possibly a malignant counterpart of basal cell adenoma. Five subtypes exist: (1) Solid, (2) Ductal, (3) Trabecular,(4) Cribriform and (5) Membranous. A solid growth, characterized by a lobular pattern with palisading of cells at the periphery of tumour islands is its foremost feature. Immunohistochemically, cytokeratin (AE1/AE3) stains all tumours, more peripherally in the solid pattern and usually centrally in the trabecular areas; vimentin shows a diffuse expression; SMA is mainly confined to peripheral tumour cells in both the solid and the trabecular growth patterns; EMA and CEA stains some of the tumours, predominantly in the luminal cells; p53 oncoprotein is focally positive in some tumours; Ki-67 stains less than 5% of the tumour cells. Staining patterns of cytokeratin and actin varies with the architecture of the tumour.[26]Separation from basal cell adenocarcinoma as shown by Nagao et al. is based on the high proliferative rates of Ki67 in basal cell adenocarcinoma as compared to Basal cell adenoma.[16]

MYOEPITHELIOMA

Sheldon was the first to describe myoepithelioma in 1943. Neoplastic myoepithelial cells are the sole components of the tumour albeit in different forms either as spindle shaped or in plasmacytoid form. Histologically myoepithelioma may either be composed of predominantly a single cell type or a combination of cell types may be noticeable. It is derived from the reserve cells of the intercalated duct. Neoplastic myoepithelial cells show immunoreactivity for S-100 protein, GFAP, vimentin, actin and CK 14 are generally positive or focally positive, but the pattern frequency of positivity is highly variable. S-100 is a reliable marker, but it lacks specificity.[27]

MYOEPITHELIAL CARCINOMA

Myoepithelial carcinoma is a rare SGN, consisting mainly of myoepithelial cells. It is characterized by EWSR1 gene aberrations, making it difficult to distinguish from Clear cell carcinoma (CCC). However, FISH has helped with this distinction by demonstrating no evidence of fusion involving EWSR1, as seen in the case of CCC. [3] While it is

considered to be chemo-resistant, a study by Shenoy (2020) demonstrated that there is evidence of fusion between EWSR1 and POU5F1, a feature in tumours arising from visceral organs. [28]Myoepithelioma can be differentially diagnosed from the myoepithelial carcinoma with the latter showing much more intense staining for p53, ki67, and PCNA as compared to the benign counterpart though the staining with other makers is also positive as that of S-100, vimentin, calponin, keratin, SMA, and GFAP.[16]

ONCOCYTOMA

Oncocytomas, described in 1932 by Jaffe are rare, slow growing tumours that most commonly arise in the parotid gland and occur in older females. Oncocytes are large cells with small irregular nuclei and dense acidophilic granules due to the presence of abundant mitochondria. Oncocytic cells are thought to originate from the transformation of epithelial cells of salivary gland ducts or acini.[29]

ONCOCYTIC CARCINOMA

Oncocytic carcinoma is an extremely rare neoplasm of the salivary glands resulting from the malignant transformation of oncocytoma. Oncocytic carcinoma can be differentiated from benign oncocytoma by the presence of a connective tissue capsule in the latter. Moreover, compared to oncocytoma, oncocytic carcinoma usually shows a greater mitotic activity and more nuclear pleomorphism.[30]Oncocytic differentiation of neoplastic cells was demonstrated by immunohistochemical positivity for mitochondrial antigen [31], keratin, alpha-1-antichymotrypsin [32].

ACINIC CELL CARCINOMA

ACC is a low grade malignant salivary gland tumour commonly occurring in the parotid gland of women with a great tendency to recur and metastasize. The genetic alterations linked to ACC of the parotid gland included alterations at chromosomes 4p, 5q, 6p, and 17p, suggesting the association of tumour suppressor genes with the oncogenesis of these tumours. Moreover, deletions of chromosome 6q, loss of Y and trisomy 21 have been reported in association with ACC [33,34]. Further molecular studies indicated that retinoblastoma pathways, which are common to most human tumours, might also be involved in the pathogenesis and etiology of ACC.[35] DOG1 is a useful IHC marker in differential diagnosis of ACC.[15]

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma (AdCC) is an indolent malignant tumour affecting both minor and major salivary glands. AdCC is subdivided into three histological groups i.e. cribriform, tubular, and solid. It presents an aggressive clinical course with early perineural invasion and local recurrence. The gene expression profile of adenoid cystic carcinoma has been studied by oligonucicotide array. The most overexpressed genes encode for basement membrane and extracellular matrix proteins of myoepithelial differentiation (e.g. laminin-ß1, versican, biglycan and type IV collagen-alpha1). The most underexpressed genes are those encoding for proteins of acinar-type differentiation (e.g. amylase, carbonic anhydrase and salivary proline-rich proteins).[36] Loss of heterozygosity in chromosome 6q23-25 has been found in 76% of cases of adenoid cystic carcinoma[16]CD43, a marker of T cells and histiocytes, has been reported to be preferentially expressed in adenoid cystic carcinomas.[37]The main genomic alteration that characterizes AdCC is the MYB–NFIB gene fusion. Overexpression of MYB is a diagnostic characteristic feature of AdCC. It is located on chromosome 6q and it encodes for a transcription factor that regulates cell proliferation and differentiation of hematopoietic, colonic, and neural progenitor cells. [12]

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands and can occur in both children and adults. It has been proposed that mucoepidermoid tumours arise from subepithelial mucus glands that line the upper respiratory and digestive tracts. If so, this might explain why this tumour type is more common at the supraglottis, which is the subsite of the larynx that has the greatest concentration of subepithelial mucous glands. The genetic aberrations involve CRTC1–MAML2 or CRTC3–MAML2 fusions, with the latter being more important [38,39]. CRTC1 is located on chromosome 9 and it encodes protein from the CREB family to enhance transcription. The CREB protein is responsible for regulating all genes involved in proliferation and differentiation. The MAML2 gene is located on chromosome 11 and it encodes for the nuclear proteins responsible for the activation of the NOTCH pathway, which is one of the most common signalling pathways activated during tumourigenesis. [12]Expression of MAML2 using FISH has been acclaimed to be very useful. It is a relatively straightforward diagnosis considering that the expression of MAML2 is exclusive to MEC.[40]

WARTHIN TUMOUR

Initially described by Hildebrand in 1895, Warthin tumour (also known as cystadenolymphoma), is a benign and frequent salivary gland neoplasm. Warthin tumour is the only benign neoplasm of salivary glands associated with smoking.[41]Initially, Hildebrand proposed that the lesion may be remnants of the branchial pouches and a variant of the lateral cervical cyst. Later, Albrech and Artz proposed the heterotropic origin of Warthin tumour from the neoplastic proliferation of salivary gland ducts present within intra- or para-parotid nodes. This theory is widely accepted and was sustained by immunohistochemistry findings, which demonstrated

that basal and luminal epithelial cells of Warthin tumour bear characteristics similar to those of the basal cells and striated duct cells of the excretory duct of the salivary gland.[42] The epithelial component is immunoreactive for cytokeratin cocktail. The lymphoid portion shows kappa and lambda light-chain polyclonality.[43]

POLYMORPHOUS LOW GRADE ADENOCARCINOMA

It's an invasive, locally destructive and neurotrophic tumour. Evans and Batsakis in 1984 coined the term PLGA which describes its variable morphological appearances and apparent low-grade behaviour.[44] PRKD1 hotspot mutations encode for p.Glu710Asp in 72.9% of PLGAs but not in other salivary gland tumours. Functional studies demonstrated that this kinase-activating alteration likely constitutes a driver of PLGA.[45] While PLGA has distinctive cytological features and a characteristic appearance of perineural invasion, its heterogeneous architecture can make for a difficult differential diagnosis with adenoid cystic carcinoma and cellular pleomorphic adenoma.[46,47]In most cases of morphologic overlap, a p63/p40 immunohistochemical panel can provide a useful adjunct for making the distinction between these clinically divergent entities.[48]

CONCLUSION

Latest developments in the field of immunohistochemistry, genetic alterations and molecular biology have helped us better in defining and diagnosing SGN. It is important for the pathologist to assess the cytoarchitectural features and profile of these neoplasms and correlate them with histogenetic and molecular concepts for better understanding which in turn will hopefully, translate into more effective therapies for prevention, local control, and cure for many of the salivary gland malignancies currently associated with notoriously protracted but lethal courses.

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