Review Article

Histogenesis of salivary gland neoplasms

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Abstract

Salivary gland tumors are one of the most complex and relatively rare group of lesions encountered in oral pathology practice. Their complexity is attributed to heterogeneity of the cells of origin of these lesions. The problem is compounded by the ability of these cells to differentiate and modify into various morphological subtypes resulting in a myraid of histomorphological patterns. This also leads to a frequent overlap of microscopic features among various neoplasms and sometimes even between benign and malignant lesions causing significant diagnostic dilemma which sometimes may even not be resolved by immunohistochemical studies. Despite this the knowledge of histogenesis and morhogenetic concepts of salivary gland tumorigenesis greatly helps the pathologist in classifying these lesions as well as determining the prognosis. It will also help in development of newer strategies for differentiating these lesions and making an early diagnosis. The present article is aimed at reviewing and summarizing the current concepts regarding the histogenesis of salivary gland tumors and their relevance to routine diagnosis and classification of these lesions.

Key Words: Histogenesis, morphogenesis, salivary gland tumor

Introduction

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.[1]

The glandular anlage first appears in the form of solid epithelial buds in the 6th embryonic week. During the 6th-8th embryonic week, the major salivary glands develop as outpouchings of oral ectoderm and grow inwardly into the surrounding mesenchyme.

There are three stages in the development of salivary glands:

In the first stage, branching dichotomous ducts develop from salivary anlage. In the second stage, the ducts acquire lumen and gland lobules form, and this continues through the 7th embryonic month. The third stage begins in the 5th embryonic month with the differentiation of the acini and further maturation of the gland, together with a considerable reduction in initially abundant connective tissue.

Early in the development of salivary glands, the primitive duct buds are composed of an inner lining of duct cells and outer myoepithelial cell layer. At later stages of development, as the branching duct system acquires spherical glandular acini as functional end units, the number of myoepithelial cells decreases until they are eventually located only at the distal segments of ducts and in primitive acini. For overall glandular growth, nervous system involvement and tightly regulated signaling pathways sonic hedgehog and the fibroblastic growth factor family of receptors are crucial.[2]

There are several controversies regarding the origin and morphogenesis of salivary gland tumors. The complexity of structure and the rarity in occurrence are a diagnostic dilemma for even experienced pathologists. The diagnostic criteria are overlapping, the classification systems are numerous, and the histopathological criteria may vary within the same tumor and in different areas of the same tumor. This article aims to review some of the concepts in histeogenesis of salivary gland tumors.

Histeogenetic Prospective

Histogenetic concepts of tumor development are now ingrained in pathology and influence decisions on the structuring of tumor classification schemes. If a histogenetic concept is attractive in that it provides a ready explanation for subjective observations in

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histological sections, then it quickly becomes accepted, frequently quoted, and eventually established as fact, even in the absence of corroborative scientific evidence.

Historical prospects

Histogenesis correctly refers to the embryological formation and differentiation of tissue/organs, in tumor pathology this term has come to imply the putative cell of origin for a particular neoplasm [Table 1].

The existence of reserve cells in normal salivary gland was originally postulated from observations of embryonic development of palatal minor salivary glands. These evolve as down growth of bilayered ducts, and it was assumed that the inner or luminal layer was derived from the outer or basal layer. This concept was based on the histological observation of developing bilayered major ducts in human fetal salivary gland. The eventual derivation of intercalated duct from these excretory ducts was also an important part of this concept.[3,4]

The semi-pleuripotent reserve cell theory was further refined and developed by Batasaki *et al*.[5,6] In an attempt to explain the histogenesis of salivary gland tumors, a bicellular theory of origin was proposed.[5,6] Two cells, the excretory duct reserve cell and the intercalated duct reserve cell, were presented as the hypothetical cells of origin for salivary gland neoplasms. It was argued that the excretory duct reserve cell gives rise to squamous cell carcinomas (SCC) and mucoepidermoid carcinomas, and that the intercalated duct reserve cell gives rise to all others. It was also shown that myoepithelial cells were responsible in part for the wide histologic variation of these neoplasms. As a highly and therefore, terminally, differentiated cell, the acinar secretory cell was said to play a minimal role in the parencymal renewal and thus, was incapable of a significant role in tumor induction.[5-7]

Although, the "bicellular theory of origin" is the most widely-accepted, but there has been little or no direct evidence to support this hypothesis. Most studies on the malignant salivary gland histogenesis claim that mucoepidermoid carcinoma, primary SCC and salivary duct carcinoma arise from the excretory duct, whereas polymorphous low grade adenocarcinoma, basal cell adenocarcinoma (BCA), adenoid cystic carcinoma (AdCC) and acinic cell carcinoma (ACC) are of intercalated duct origin.[8,9] Adenocarcinoma, not otherwise specified (NOS) (AdC NOS) is assumed to arise from either of these reserve cells[10,11] and carcinoma ex pleomorphic adenoma is of uncertain histogenesis.[12]

In a continually renewing cell population, stem cells can be regarded as a reservoir of cells with a high capacity for self-renewal that gives rise to all differentiated progeny. They are the primary source for the generation and maintenance of cellular diversity and tissue homeostasis. In general, neoplasms manifest differentiation pathways similar to those found in the development and renewal of the normal tissues from which they arise. This feature serves as a basis for classification schemes of neoplasms and as in the normal tissues, there is usually an inverse correlation between proliferativecapacity and differentiation within the neoplasms

Multicellular histogenetic concept

It was proposed that differentiated cells at all the levels of the gland, including acinar and basal cells are capable of cell division. When autoradiography of neonatal rat salivary gland after tritiated thymidine administration was done, electron microscopy of these tissues revealed that duct basal cells, luminal cells at all levels of duct system and even acinar cells were capable of DNA synthesis and mitosis. Indeed, in these studies more luminal than basal cells were seen in mitosis.[13,14] In adult rat when salivary gland was induced to undergo hyperplasia and it was found that more acinar cells than intercalated duct cells were found in S phase of the cell cycle. Similar findings were also reported in fetal and adult human salivary gland.[15,16] From such observations it was evident that dividing cells were not limited to basal cells of excretory ducts and luminal cells of intercalated ducts thus there was no support for the semi-pluripotential bicellular reserve cell hypothesis.[17]

However, there is considerable evidence for a multicellular theory of tumor histogenesis. That is, any of "multiplicity of cell types in normal salivary gland

Table 1: Histogenetic concepts of salivary gland tumors

Histogenesis theories proposed by various authors	Proposed hypothesis
Basal reserve cell theory	Basal cells of both excretory and intercalated ducts responsible for differentiation of functional units
Pluripotent unicellular reserve cell theory	Basal cells of excretory duct are responsible for the development of all remaining salivary gland units
Semipleuripotent bicellular reserve cell theory: Advanced by Eversole 1971 and further refined and developed by Batasakis *et al*.	The outer (basal) layer of cells gave rise to inner (luminal) layer. The eventual derivation of intercalated ducts from these excretory ducts was proposed
Multicellular theory	Differentiated cells at all the levels of the gland, including acinar and basal are capable of cell division

have the potential to give rise to any of various types of tumors occurring in this organ."

In terms of tumor induction, it should be appreciated that "differentiated cells are capable of metaplastic alterations" e.g., epidermoid metaplasia has been demonstrated in acinar and myoepithelial cells of the salivary gland of the rat and in secretory cells of hamster tracheal mucosa.[18] The role of repair and replenishment could be assumed only by uncommitted stem (reserve) cells, and by inference, such as cells are solely at risk for neoplastic induction.[19]

Oncogenesis presumably occurres at various stages of the morphogenetic process necessary for full differentiation of the various normal cell types, giving rise to a range of tumor types and their varying degrees of differentiation.[6,20]

Current histogenetic classification of salivary gland tumors is based on the hypothesis that repair and replacement of terminally differentiated components of salivary gland such as duct epithelium and acinar cells are totally dependent on reserve or stem cells.[14,15] However, in adults the weight of evidence indicates that cell renewal and gland regeneration are functions of each of the various cell types in salivary gland, i.e., acinar cells, as they form the bulk of the gland parenchyma, present the greatest proportion of cycling cells in rat and human salivary glands. Though definitive evidence for the reserve cell hypothesis continues to be unavailable.[6,19,20]

Salivary gland tumors, like tumors arising in other tissues, are classed on the basis of the differentiation properties of the tumor cells. For the pathologist, it is this differentiation process and the architectural arrangement of the tumor cells that are the keys to classifying a particular salivary gland tumor. On this basis of, it becomes immaterial to attempt to predict from what segment of the duct system a particular tumor originates. This is the reason for stressing investigation of morphological processes as central to developing appropriate and consistent diagnostic criteria for the subtypes of salivary gland tumors.[21]

Morphogenetic concepts

Regardless of the cell of origin for salivary gland tumors, it is essential to appreciate the role of tumor cell organization, the type of cell differentiation, and the material synthesized by the cells and their placement within the tumor. Rather than emphasizing on the resemblance of particular salivary gland tumors to certain segments of the salivary gland secretory or excretory segments, it is more useful to appreciate underlying patterns of differentiation within the morphologically distinctive neoplasms.[20]

Evaluation of tumors based on tumor cell phenotype(s), their arrangement, and the unique production of stromal materials that influences the final histology in these tumors allows for the establishment of improved diagnostic criteria.[1,22,23]

A number of factors affect the histologic feature of salivary gland tumors. In many cases, patterns of tumor differentiation reflect the bilayered cells composed of luminal or acinar cells and outer basal and/or myoepithelial cells. This histologic aspect is called ducto-acinar concept.

The salivary gland exhibits two-tiered organization, which comprises luminal (acinar and ductal cells) and abluminal (myoepithelial and basal cells). The secretory acini and the intercalated ducts are wrapped by myoepithelial cells. The straited ducts and the down streaming conducting units are lined by simple or pseudostatified columnar epithelium which gradually transforms into the stratified squamous epithelium, in the salivary duct, and they are supported by basal cells.

Batasaki has been instrumental in emphasizing the bicellular constitution (luminal and neoplastically modified myoepithelial cells) of certain salivary gland tumors; these include pleomorphic adenoma, AdCC, epithelial myoepithelial carcinoma, and terminal duct carcinoma. This feature has been extended to additional types of salivary gland tumors, such as certain monomorphic adenomas and ACC, mucoepidermoid carcinomas, malignant mixed tumor and Warthin's tumor. In salivary gland tumors, 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 cell form such as spindle, plasmacytoid, epithelial, and clear.[1]

Myoepithelial cells are physiologically and functionally modified epithelial cells located between the luminal cells and basement membrane. They are stellate shaped with cytoplasmic processes embracing the acini, or spindle shaped surrounding the intercalated ducts. They possess a dual epithelial and smooth muscle phenotype characterized ultrastructurally by the presence of desmososmes, intermediate filaments, pinocytic vesicles and myofilaments. Myoepithelial cells produce an extracellular matrix such as basement membrane materials and myxoid substances leading to diverse histology of salivary gland tumors. They may also exert an anti-invasive effect in a neoplasm promoting epithelial differentiation, secreting proteinase inhibitor and suppressing angiogenesis.

Modification of myoepithelial cell component is also evident from the immunohistochemical studies.

Intermediate filament vimentin and glial fibro acidic protein are not expressed in the normal myoepithelium, both are readily detected in modified myoepithelial cells of pleomorphic adenoma and myoepitheliomas.

P-63, high molecular weight cytokeratin (CK-14) are positive for myoepithelial cells. Other myoid markers are calponin, actin, myosin, S-100 and Glial Fibro Acidic Protein (GFAP). The luminal cells are readily highlighted by immunostaining for cytokeratin, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA). CD117/c-kit is negative in the normal salivary gland cells, however, is interestingly positive in the luminal (glandular) cells of various types of salivary gland tumors.

The abluminal cells of the striated ducts, excretory ducts, and salivary ducts are basal cells that differs ultastructurally from myoepithelial cells in the absence of myofilaments. They maintain the capacity of multidirectional differentiation and play an important role in regeneration and metaplastic changes. They are immune reactive for p-63 and high molecular weight cytokeratin, but are negative for myoid markers like S-100 and GFAP.[24]

Cell differentiation results in three basic models of benign or malignant salivary gland neoplasms.[1]

1. In one form of differentiation, tumor cell population results in a dual population that combines recognizable luminal and/or acinar cells with myoepithelial and/or basal cells
2. A second pattern results primarily in luminal/glandular cells that resemble to some extent normal duct epithelial and/or acinar cells
3. The third process produces tumor cells resembling normal myoepithelial and/or basal cells.

Some salivary gland tumors display an overlap in terms of cellular differentiation.

For example, neoplastic myoepithelial cells in both AdCC and basal cell adenoma can participate in formation of glandular lumens. This observation emphasizes the central role of tumor cell differentiation in these neoplasms, as it suggests that any tumor cell has the potential to differentiate into at least two directions-ductal or myoepithelial/basal-or assume a hybrid form.

Dardick and Van Nostrand[23] reviewed the three potential mechanisms for the derivation of new secretory or other specialized cells of the duct system:

1. Replication or mitotic division of existing fully differentiated cells,
2. Differentiation from a population of uncommitted stem cells or committed precursor cells, and
3. Transformation or the process of metaplasia in, which one type of specialized cell modifies to assume characteristics of another cell type.

Primarily, monocellular salivary gland tumors are composed either of luminal type cells, with or without acinar differentiation or of the neoplastic counterpart of myoepithelial and/or basal cell [Figure 1].

These models depict the three basic forms of salivary gland tumors:

1. Involves differentiation of duct luminal cells plus basal-like and/or myoepithelial-like cells;
2. It Reveals only duct luminal and/or acinar cells; and
3. It is composed solely of myoepithelial-type and/or basal-like tumor cells.

The presence or absence of significant amounts of specifically localized proteoglycans, basal lamina, other collagens and elastin in relation to the neoplastic myoepithelial/basal cells provides the other major criterion for classification [Figure 2].

In addition to the combinations of luminal and myoepithelial/basal cell differentiation in these tumors, the type and extent of synthesis as well as the distribution of extracellular materials considerably influence the final histology of salivary gland tumors. The presence or absence of significant amounts of specifically localized proteoglycans, basal lamina, other collagens, and elastin in relation to the neoplastic myoepithelial/basal cells provides the other major criterion use-in describing these tumors for classification purposes [Table 2].

Accumulated basal lamina and glycosaminoglycans may be present in certain bi-cellular and predominantly myoepithelial/basal cell neoplasms and absent in others. Both the degree of synthesis of these materials and the nature of their containment between the myoepithelial and/or basal cell compartment influences the final morphology of a particular salivary gland tumor class. In AdCC, well-controlled localization of proteoglycans and basal lamina occurs, whereas in pleomorphic adenoma, excessive production forces separation of adjacent tumor cells and the eventual development of myxochondroid zones.

Conclusion

Salivary gland tumors are relatively rare and diverse group of lesions with unresolved intricacies from its development to maturation. The pathologists usually encounter benign neoplasms and very few experience full range of salivary cancers which are best managed in specialist centers.

The modern approach is more realistic, in that histological typing is based on cellular differentiation rather than cell of origin.

Immunohistochemical staining has only limited role in diagnosis of salivary gland tumors.

Its main applications are:

1. To delineate whether there is two cell type differentiations in tumors with complex architecture. Demonstration of EMA or CEA may help to highlight ductal structures (glandular lumina) in the solid variant of AdCC, cellular pleomorphic adenoma, the solid form of epithelial myoepithelial carcinoma, and BCA
2. To confirm the diagnosis of myoepithelioma/ myoepithelial carcinoma by demonstrating markers such as calponin and actin
3. Ki-67 proliferative index may be useful in distinguishing an adenoma from a carcinoma (Ki-67 index usually <5% versus >10%).

Recently, CD117 have been shown to help in highlighting the luminal cell component of various salivary gland tumors, whereas p63 or maspin can aid in highlighting the abluminal cell component.[25]

Salivary gland tumors offer a mydraid of diversity thus maintaining the ambiguity of these neoplasms. Still the enigma of diagnosing the salivary gland tumors continues challenging Oral Pathologists in routine practice. It is important for the pathologist to assess the cytoarchitectural features and cytoarchitectural profile of these neoplasms and correlate them with histiognetic concepts for better understanding which in turn will help in diagnosis and management of these lesions.

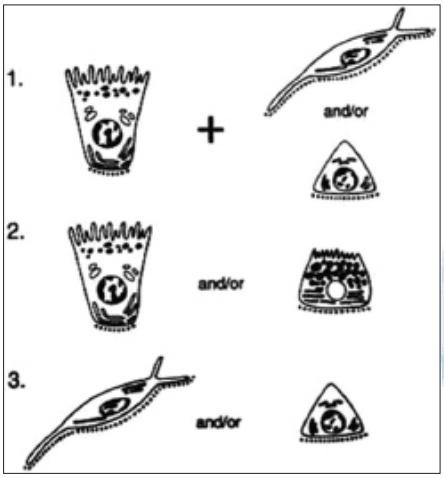

Figure 1: Models depicting common cytodifferentiation pathways in salivary gland tumors

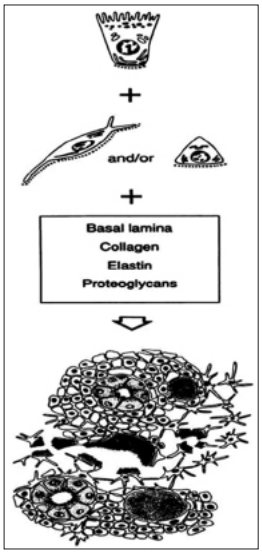

Figure 2: Model depicting in addition to the combinations of luminal and myoepithelial/basal cell differentiation in these tumors, the type and extent of synthesis as well as the distribution of extracellular materials considerably influence the final histology of salivary gland tumor

Table 2: Proposed taxonomic classification of salivary gland tumors

Classification of neoplasm	Subclassification of neoplasms	Benign neoplasm	Malignant neoplasm
Neoplasm composed of luminal and modified myoepithelial cells	Histologically with apparent proteoglycan and basal lamina production Histologically lacking obvious proteoglycan and basal lamina production	Pleomorphic adenoma Basal cell adenoma Basal cell adenoma Cellular pleomorphic adenoma Warthin's tumor	Malignant mixed tumor Adenoid cystic carcinoma (cribriform) Basal cell adenocarcinoma Adenoid cystic carcinoma (solid/tubular) Epithelial myoepithelial carcinoma Mucoepidermoid carcinoma Polymorphous low grade carcinoma
Neoplasm composed primarily of myoepithelial/basal cells		Myoepithelioma	Myoepithelial carcinoma
Neoplasm composed primarily of luminal/ acinar cells		Canalicular adenoma Ductal papillomas Cystadenoma Oncocytoma	Acinic cell carcinoma Salivary duct carcinoma Adenocarcinoma, NOS Oncocytic carcinoma
Neoplasm composed of undifferentiated cells			Undifferentiated carcinoma Small cell carcinoma

NOS=Not otherwise specified

References

1. Dardick I. Histogenesis and Morphogenesis of salivary gland neoplasms. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical Pathology of the Salivary Glands. Philadelphia: W.B. Saunders; 1991. p. 108.
2. Jaskoll T, Leo T, Witcher D, Ormestad M, Astorga J, Bringas P Jr, *et al*. Sonic hedgehog signaling plays an essential role during embryonic salivary gland epithelial branching morphogenesis. Dev Dyn 2004;229:722-32.
3. Eversole LR. Histogenic classification of salivary tumors. Arch Pathol 1971;92:433-43.
4. Attie JN, Sciubba JJ. Tumors of major and minor salivary glands: Clinical and pathologic features. Curr Probl Surg 1981;18:65-155.
5. Regezi JA, Batsakis JG. Histogenesis of salivary gland neoplasms. Otolaryngol Clin North Am 1977;10:297-307.
6. Batsakis JG. Salivary gland neoplasia: An outcome of modified morphogenesis and cytodifferentiation. Oral Surg Oral Med Oral Pathol 1980;49:229-32.
7. Batasaki JG, Chinn EK, Weimert TA, Work WP, Krause CJ. Acinic cell carcinoma: A clinicopathological study of 35 cases. J Pathol 1986;148:307-20.
8. Batsakis JG, Luna MA. Low-grade and high-grade adenocarcinomas of the salivary duct system. Ann Otol Rhinol Laryngol 1989;98:162-3.
9. Batsakis JG, Wozniak KJ, Regezi JA. Acinous cell carcinoma: A histogenetic hypothesis. J Oral Surg 1977;35:904-6.
10. Eversole LR. Histogenic classification of salivary tumors. Arch Pathol 1971;92:433-43.
11. Batsakis JG, el-Naggar AK, Luna MA. Adenocarcinoma, not otherwise specified: A diminishing group of salivary carcinomas. Ann Otol Rhinol Laryngol 1992;101:102-4.
12. Tortoledo ME, Luna MA, Batsakis JG. Carcinomas ex pleomorphic adenoma and malignant mixed tumors. Histomorphologic indexes. Arch Otolaryngol 1984;110:172-6.
13. Denny PC, Chai Y, Pimprapaiporn W, Denny PA. Three-dimensional reconstruction of adult female mouse submandibular gland secretory structures. Anat Rec 1990;226:489-500.
14. Denny PC, Chai Y, Klauser DK, Denny PA. Three-dimensional localization of DNA synthesis in secretory elements of adult female mouse submandibular gland. Adv Dent Res 1990;4:34-44.
15. Walker NI, Gobé GC. Cell death and cell proliferation during atrophy of the rat parotid gland induced by duct obstruction. J Pathol 1987;153:333-44.
16. Walker NI, Pound AW. An autoradiographic study of the cell proliferation during involution of the rat pancreas. J Pathol 1983;139:407-18.
17. Dardick I, Jeans MT, Sinnott NM, Wittkuhn JF, Kahn HJ, Baumal R. Salivary gland components involved in the formation of squamous metaplasia. Am J Pathol 1985;119:33-43.
18. Sigler RE, Newkirk C, McDowell EM. Histogenesis and morphogenesis of epidermoid metaplasia in hamster tracheal organ explant culture. Virchows Arch B Cell Pathol Incl Mol Pathol 1988;55:47-55.
19. Burford-Mason A, Dardick I, van Nostrand P. Salivary gland neoplasms – Stem cell histogenesis? J Laryngol Otol 1990;104:521-3.
20. Batsakis JG, Ordonez NG, Ro J, Meis JM, Bruner JM. S-100 protein and myoepithelial neoplasms. J Laryngol Otol 1986;100:687-98.
21. Dardick I, Burford-Mason AP. Current status of histogenetic and morphogenetic concepts of salivary gland tumorigenesis. Crit Rev Oral Biol Med 1993;4:639-77.
22. Dardick I, van Nostrand AW. Myoepithelial cells in salivary gland tumors – Revisited. Head Neck Surg 1985;7:395-408.
23. Dardick I, van Nostrand AW. Morphogenesis of salivary gland tumors. A prerequisite to improving classification. Pathol Annu 1987;22:1-53.
24. Cheu W, Chan JK. Salivary gland tumours. In: Fletcher CD editor. Diagnostic Histopathology of Tumours, 2nd ed. London: Churchill Livingstone; 2000. p. 231.
25. Cheuk W, Chan JK. Advances in salivary gland pathology. Histopathology 2007;51:1-20.

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