An Insight into Histogenesis and Morphogenesis of Salivary Gland Neoplasm

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Abstract

Introduction: Salivary gland tumors are complex and diagnosing them remains a challenge due to their varied histomorphology attributed to the ability of cell to differentiate from its cell of origin and transform into various morphological patterns.

Aim: The present article is aimed at reviewing the current concepts in tumorogenesis of salivary gland lesions emphasizing on the aspect of histogenesis and morphogenesis.

Materials and Method: The relevant article was collected and reviewed

Discussion: The current concepts of histogenesis and morphogenesis in the development of tumor may help the pathologists to differentiate the salivary gland tumors and to diagnose at the earliest.

Conclusion: Understanding the insight of histogenesis of salivary gland will help to set criterias for classification of tumors based on cell of origin and the morphological patterns.

Keywords: salivary gland, histogenesis, morphogenesis


Introduction

Salivary glands hold the most histologically heterogeneous group of tumors with greatest diversity of morphologic features. Recognition of a specific cell or the numerous cell types in salivary gland tumors is therefore, one key to the correct diagnosis. Standards that define the limitations for each subtype are needed for reliable and accurate diagnosis of salivary gland tumours. Given the vast histomorphology for most subtypes and the wide diversity in histology from tumour to tumour, is not an easy process. Different approaches of conceptualising the evolution and differentiation of the numerous variations exist.

Histogenesis [Gr histos web (a combining form denoting relationship to tissue) and Gr genesis production] is the development of tissues from undifferentiated cells of an embryo.

In pathology, this phrase has evolved to be associated with the “cell of origin” for a neoplasm rather than the tumor’s developing phase.

Although histogenesis refers to the embryological development and differentiation of tissue/organs, it has come to mean the presumed cell of origin for a specific neoplasm in tumour pathology.

Morphogenesis (Gr. Morphe - form and gennan to produce) is the development of the form of a certain organ of individuals who achieve the type, that the majority of the species’ individuals approximate.

For pathologists, this definition refers to the process of differentiation that grows naturally in neoplasms and the histopathology that arises. Morphogenesis is concerned with the final form and structure that pertains to embryological development and differentiation.

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Histogenetic Concepts:

- Salivary gland tumours focus on the two types of normal duct cells that are thought to be the exclusive source of certain tumour classifications and individual tumours. Such a theory ignores the apparent origin of certain salivary gland tumours, as well as the successive developmental processes that tumours go through, which can have a significant impact on histomorphology at the time the lesion is reached.  

  Current histogenetic classification schemes have two core dogmas that need to be reviewed.

  Tumor induction is thought to be lacking in acinar cells, which are regarded terminally differentiated and thus unable to divide further. (Regezi and Batsakis 1977; Batsakis et al 1989).  

  Completely differentiated cells can lose their functional features through dedifferentiation and fully differentiated cells can change their functional qualities through transdifferentiation. (Regezi and Batsakis 1977; Batsakis et al 1989).

Principal Cell types and their Organization:

- Despite the glands’ intricate cellular differentiation, it’s wise to think about them as having two primary categories of cells: luminal and basal, grouped in a specific and presumably functional connection for descriptive reasons. (Figure. 1)

Luminal Cells

- Luminal cells are secretory cells that make up acini, as well as the ductal system’s lining or lumen-forming cells, which are found in many salivary gland tumours, either alone or in combination with non-luminal cells. Luminal cell formation, organisation, and type, whether alone or in combination with other cells, have a significant impact on final histomorphology.

- The complex and occasionally varied cytokeratin patterns seen in luminal cells at various levels of the duct system in the parotid and submandibular glands support their variable differentiation.  

  It is self-evident that acinar cells differentiate into both serous and mucinous cells, with secretory granules having variable ultrastructural appearances depending on the gland. This variation and range of cytomorphology in the normal gland has consequences for the histomorphology spectrum in salivary gland tumours.

Basal/ Myoepithelial Cells

- Human salivary glands comprise basal or myoepithelial cells on the outer surface of all levels of the ducts, as well as acinar units.

  In excretory ducts, cuboidal-shaped basal cells form a nearly continuous layer, but when the striated ducts become intralobular, they gradually become a discontinuous layer. Cuboidal basal cells coexist with triangular-shaped cells and typically designed myoepithelial cells in some striated ducts, which is quite remarkable. The latter is still discontinuous, and it is the intercalated duct’s and acinus’s main basally situated cell.

  Salivary gland basal cells lack specialised ultrastructural characteristics. Because of their undifferentiated appearance, it has been suggested that they are “reserve” or “stem cells” in salivary gland tumours, and that a primitive ultrastructural appearance of tumour cells at basal sites equates to a reserve cell. Nonetheless, when it comes to cell recognition and naming in salivary gland cancers, it’s still helpful to think of myoepithelial and basal cells as a single entity. It’s simpler to detect how tumour cells on the outside of ducto glandular structures in these tumours can exhibit a range of differentiation, from basal cells on one end of the spectrum to myoepithelial cells on the other, as determined by immunocytochemistry and light and electron microscopy. These cells have a wide range of shapes morphologically.

Features and Relationships of Myoepithelial and Basal Cells

- Interrelationships between normal myoepithelial and basal cells must be understood to see if they influence salivary gland tumour differentiation processes.

  Despite the fact that myoepithelial and basal cells share a large number of cytokeratin filaments with duct luminal cells, one of these filaments, cytokeratin 14 (CK14), is not immunocytochemically detectable in acinar or luminal cells.

  Despite anatomical differences, intercalated duct myoepithelial cells, acini, and basal cells of all duct segments exhibit cytokeratin-14. Perhaps these two cell types have a similar ancestor during gland development and cellular differentiation.

- Basal cells of the major interlobular and main excretory ducts are nearly continuous, but basally located cells on other segments of the excretory duct and at all levels of the striated ducts are intermittent.

  Compared to the more varied, irregularly contoured, podocyte-like myoepithelial cells associated with acini, myoepithelial cells associated with intercalated ducts appear to be regularly and closely aligned longitudinally with a spindle shape. From the distal acini to the proximal excretory duct, myoepithelial and basal cells form a continuum, at least with intermediate filament-marker cytokeratin-14.

The Ducto-Acinar Unit:

- Dardick et al proposed the ducto-acinar unit as the basic architectural structure of pleomorphic adenomas in 1983 after surveying the ultrastructural features of a series of pleomorphic adenomas to explain the wide range of histology both between and within subtypes of these tumours.

  Well organised luminal epithelial cells forming duct-like structures surrounded by more separated and irregularly shaped tumour cells are a basic and repetitive configuration and a caricature of the architectural arrangement of ducto-acinar units in the normal gland in lower electron microscopy graphs of pleomorphic adenomas and adenoid cystic carcinomas.

  By using the ducto-acinar unit as a basic structural tumour component, it is possible to appreciate common developmental patterns in salivary gland tumours and to comprehend their complex histology, as well as the reasons for overlapping morphologic patterns that cause problems in differential diagnosis and the interrelationship of the various subtypes for classification purposes.

Relationships of Acinar and Duct Luminal Cells

- Despite their epithelial character, the cytoplasm of acinar cells, whether serous or mucous, immunocytochemically shows little or no cytokeratin filaments.

- Luminal cells at all levels of the duct system, on the other hand, are consistently and intensely immunostained for cytokeratin filaments.
• Acinar cells, another type of luminal cell, have a lot of cytologic variety, usually in the form of secretory granules and a full complement of organelles. The incremental modification in the continuum from acinar cells to excretory duct luminal cells, as well as morphological variations in luminal cells in salivary glands, have an impact on neoplastic luminal cell differentiation in salivary gland tumours.3

Synthesis of Extracellular and Other Proteins
• The creation of lobules in the embryonic salivary gland is dependent on the synthesis of extracellular components such as glycosaminoglycans and collagens. Although the causes are likely unrelated in salivary gland malignancies, comparable components such as basal lamina and glycosaminoglycans play an important role in the histomorphology of tumours like pleomorphic adenoma and adenoid cystic carcinoma.3

Morphogenetic Concepts:
• This concept is significant because it directly connects the histology of neoplastic behavior transformation to the classification of salivary gland tumours, rather than designating a specific cell or cells of origin, which is difficult to pinpoint once the tumour is clinically visible and thus remains speculative.1
• On the other hand, focuses on tumour cell differentiation and other cellular changes that critically influence the histomorphology at the time of biopsy or excision, despite the fact that tumour initiation mechanisms are important and likely influence many aspects of tumour development. The particular traits that allow histologic recognition of each normal organ and tissue are determined by morphogenetic changes.3

It is feasible to recognise the progression of histological features in salivary gland tumours by understanding the ducto-acinar concept, which is necessary for accurate morphological classification. Rather than focusing on the similarities between specific salivary gland tumours and specific secretory or excretory segments of the salivary gland, it is more useful to appreciate underlying patterns of differentiation within the morphologically distinct neoplasms as defined by current classifications (Ellis et al 1991, Seifert and Sobin, 1991).4

Using the normal salivary gland ducto-acinar unit as a model, salivary gland tumours can be divided into two broad categories: one a caricature of the normal gland with two basic cell types, neoplastic luminal and myoepithelial or basal cells, and the other differentiating either neoplastic luminal cells or myoepithelial and/or basal cells.

Luminal-type cells with or without acinar differentiation, as well as the neoplastic counterparts of myoepithelial and/or basal cells, make up the majority of monocellular salivary gland cancers. 4 In respect to the neoplastic myoepithelial/basal cells, the presence or absence of considerable numbers of para-

Fig. 1: Diagram showing various structural units of salivary gland.

Fig. 2: Taxonomy of salivary gland tumours

Fig. 3: The morphological units arising from excretory duct reserve cell progenitor
particularly localised proteoglycans, basal lamina, other collagens, and elastin offers the other primary criterion useful in defining these tumours for classification purposes. Some bicellular, mainly myoepithelial/basal cell neoplasms have accumulated basal lamina and glycosaminoglycans, while others do not. The advanced morphology of a given salivary gland tumour class is influenced by both the degree of synthesis of these materials and the manner of their confinement between the myoepithelial and/or basal cell compartments.

- Based on a growing body of knowledge about systematic and comparative studies of salivary gland tumours, a taxonomic flow chart can be created that can be used to define diagnostic criteria for the diverse group of neoplasms that arise in these glands.

**Taxonomy of Salivary Gland Tumors** (Figure 2)

Four theories have been hypothesized for the histogenesis of salivary gland tumors:

- **Basal Reserve Cell Theory**
- **Pleuripotential Unicellular Reserve Cell Theory**
- **Semipleuripotential Bicellular Reserve Cell Theory**
- **Multicellular Theory**

**Basal Reserve Cell Hypothesis:** The existence of reserve cells in normal salivary glands was first proposed by Eversole in 1971 based on observations of embryonic development of palatal minor salivary glands. The inner or luminal layer is thought to be formed from the outer or basal layer as these develop as downgrowths of bilayered ducts. These findings led to the designation of basal cells as reserve cells, owing to their ability to function as stem cells, notably in the formation of duct luminal and acinar cells. Regezi and Batsakis accepted and popularised the reserve cell notion as the fundamental mechanism for the histogenesis of salivary gland malignancies in 1977. Although Eversole (1971) linked pleomorphic adenoma to the excretory duct reserve cell without explanation or apparent rationale, in the change presented by Regezi and Batsakis, the intercalated duct reserve cell became the histogenetic source for this

![Fig. 4: Cell of origin of various cells of salivary gland](image)

![Fig. 5A & B: The stochastic model of differentiation is illustrated in (a) the progenitor cell (dm) gives rise to cells d and m committed to the two pathways of differentiation. B: The sequential model of differentiation wherein the two potentials for differentiation are expressed sequentially rather than having diversified along two distinct pathways illustrated in (b)](image)

**Table 1:** cell of origin for various hamartomas, adenomas and adenocarcinomas.

<table>
<thead>
<tr>
<th>CELL OF ORIGIN</th>
<th>DIFFERENTIATION</th>
<th>HAMARTOMA</th>
<th>ADENOMA</th>
<th>ADENOCARCINOMA</th>
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<tr>
<td>Excretory duct Reserve cell progenitor</td>
<td>Squamous</td>
<td>Intraductal papilloma</td>
<td>Pleomorphic adenoma</td>
<td>Epidermoid carcinoma, Mucoepidermoid carcinoma</td>
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<td></td>
<td>Squamous, acinar, ductal</td>
<td>Intraductal papilloma</td>
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<tr>
<td>Intercalated duct cell progenitor</td>
<td>Intercalated duct</td>
<td>Canalicular adenoma</td>
<td>Monomorphic</td>
<td>Cylindroma, adenocarcinoma</td>
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<td></td>
<td>Striated duct</td>
<td>Warthin’s tumor</td>
<td>Adenoma</td>
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<td>Acinar cell</td>
<td>Oncocytoma</td>
<td>Cystadenoma</td>
<td>Acinic cell adenocarcinoma</td>
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<td>Acinic cell nevus</td>
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Differentiated cell types in adult salivary glands were thought to be incapable of undergoing neoplastic change, acinar and striated duct maintenance was thought to be achieved by a low level of mitotic activity in these fully mature or "end-differentiated" cells (Batsakis, 1990). Uncommitted stem (reserve) cells were the only ones capable of repair and replenishment (Batsakis, 1990), implying that they were the only ones susceptible to neoplastic induction.1

Pleuripotent unicellular reserve cell theory: Eversole published his dissertation on salivary gland tumour histogenetic classification in 1971. Basal reserve cell hypothesis and Pleuripotent unicellular theory were the first two theories proposed.5

According to the pleuripotent unicellular theory, all cells originate from the reserve cell progenitor, and the neoplastic transformation of this cell causes all salivary gland tumours. The emergence of certain tumours is most likely linked to the development of possible differentiation factors. It's been proposed that the excretory duct reserve cell can produce squamous or epidermoid elements, or that it has the ability to produce intercalated duct cells and hence acinar elements. According to this view, all salivary gland tumours are caused by excretory duct basal cells.5 (Figure 3)

Semipuripotent bicellular reserve cell theory: Influencing modern theories of salivary gland tumour development Eversole proposed one such concept in 1971, based on histological observations of developing bilayer major duct human foetal salivary glands, with the implication that the outer (basal) layer of the cells gave rise to the inner (luminal) layer. The eventual derivation of intercalated ducts from these excretory ducts was also a key feature of this well-accepted and established theory. Bataki and colleagues expanded this hypothesis further, proposing that excretory duct reserve (basal) cells originate only in a few tumours, such as MEC and SCC, whereas intercalated duct (luminal) cells are responsible for lesions such as PA, MA, ADCC, and ACC as highly terminally differentiated. Because acinar secretory cells only play a minor role in parenchymal regeneration, to play a large role in tumour induction.5 (Figure 4) (Table 1)

Neoplastic transformation of salivary epithelium

- Malignant transformation of reserve cells that retain the ability to generate intercalated duct-like elements can then produce mucous and columnar elements as well as epidermoid cells as a secondary effect. The degree of differentiation encountered here will determine whether high- or low-grade mucoepidermoid carcinoma occurs, depending on the capacity of these reserve cells.3,4
- Oncocytoma and Warthin's tumour, papillary cystadenoma, and papillary cystadenocarcinoma are all examples of hamartomatous, benign neoplastic, and malignant neoplastic alterations of intercalated duct cells with differentiation towards striated ducts.
- Adenoid cystic carcinoma or cylindroma might emerge from the malignant transformation of intercalated duct cells and subsequent differentiation. The stratification could be the result of intercalated duct cells' failed attempts to form acinar or striated ducts. The presence of mucin within cell nests is consistent with intercalated duct cell origin, as this cell may have secretion granules in its normal condition.1,3,5

- This notion varies from the unicellular concept in that intercalated duct cells are the only progenitor cell types that can exist.1
- Dardick came to the conclusion that dividing cells are not restricted to excretory duct basal cells and intercalated duct luminal cells. As a result, there is no evidence to support this theory.
- Several cell kinetics studies have failed to show a single cell type, such as basal cells, as proposed in the semipuripotent bicellular idea, and their differentiation pathways as the sole mechanism in normal glands, glandular hyperplasia, or regeneration.7

Multicellular theory

According to this idea, all types of salivary gland cells, including duct luminal, duct basal, acinar, and myoepithelial cells, are capable of cell division (although to varying degrees) even in adulthood. Experiments show that luminal epithelial cells can undergo mitosis, which is significant because this region of the duct system is excluded from current concepts of tumour induction in the salivary gland. Furthermore, both basal and luminal epithelial cells or the excretory ducts can divide, a feature not predicted by the reserve cell hypothesis.1

Growing data suggests that all types of cells in the normal salivary gland, from foetal through adulthood, may divide and that this ability is not limited to certain cells in specific sites.

Basal cells of the striated and excretory ducts constitute a heterogeneous population in terms of cytokeratin and actin filament complements, suggesting that they may have additional functional and structural responsibilities.4

The creation of epimyoepithelial islands in benign lymphoepithelial lesions and squamous metaplasia in chronic sialadenitis, on the other hand, is attributable to preferential proliferation of the duct system's basal cells. Basal cells in a normal salivary gland are thus a functionally complicated unit with a possible purpose that goes beyond what is currently thought of them. This, together with evidence that all types of salivary gland cells can divide, makes the Multicellular Theory a more feasible histogenetic paradigm, especially in terms of tumour initiation in the adult gland.5

Role of stem cells

- Although salivary gland neoplasms exhibit a complicated pattern of tumour cell development and structure, histogenetic models have largely relied on reserve or stem cells.7 Stem cells are a pool of cells with a strong ability for self-renewal that give rise to all differentiated progeny, including duct cells, acinar cells, and myoepithelial cells. They are the primary source of cellular diversity and tissue homeostasis production and maintenance. The stem cell theory assumes the existence of a permanent pool of stem cells, or a reserve cell population, that serves as a reservoir for cell replenishment in order to maintain morphological and functional integrity, or, in the case of neoplasm, a perverted and abnormal condition.

Although no definitive definition of stem reserve cells has been achieved in any organ system, growing experimental evidence strongly suggests that they play a role.1,5 The development of salivary gland neoplasms may be regarded as an epigenetic event triggered by an oncogenic stimulus onto morphologic and cellular differentiation in a manner analogous to stages in embryonic and early postnatal development of glands.
in that case the development of salivary gland neoplasms may be regarded as an epigenetic event triggered by an oncogenic stimulus onto morphologic and cellular differentiation.¹

**Stem Cells and Oncogenesis of Salivary Neoplasms**

- Rudland has combined the stem cell idea with oncogenesis as an abnormal event of development or regeneration, as well as the key modifying role of myoepithelium in a hierarchy of exocrine gland neoplasms (1987).
- His research with a variety of neoplastic, proliferative, and developmental models all lead to neoplasms being caused by a mutation in stem cells. The mutation results in a stochastic or sequential truncation of the cell’s normal differentiation processes. Following the truncation, cells are produced that alter gene expression at a considerably faster rate than in a proliferative or developmental phase.
- One advantage appears to be a preferential selection of cells that have lost their ability to differentiate into myoepithelial cells in salivary gland neoplasms.
- As the metastatic potential of the neoplasms increases, myoepithelial cell characteristics and their related basement membranes are gradually lost, or absent.
- Biologically high-grade carcinomas of the salivary duct system, such as salivary duct and high-grade mucoepidermoid carcinomas, lack myoepithelium, whereas biologically low-grade carcinomas, such as terminal duct and epi-myoeplithelial carcinomas, contain myoepithelial cells as integral constituents. (Figure 5A and 5B).
- Whether generative cells in the salivary glands’ terminal duct system are labelled as stem, reserve, basal, transitional, or undifferentiated, they remain a regenerative pool and oncogenic targets. On the one hand, the cells take on myoepithelial cell shapes, while on the other, they take on epithelial cell forms. On the basal surface of myoepithelial cells, there is a gradual accumulation of myofilaments, hemidesmosomes, micropinocytic vesicles, and basement membrane, resulting in a gradation in immunocytochemical phenotype and ultrastructure. Apical microvilli, unique junctional complexes, and secretory products distinguish epithelial cells from each other in immunocytochemical phenotype and ultrastructure.

Indeed, many types of salivary gland neoplasia are likely not as distinct as classification methods suggest, and within salivary neoplasms, not only one histopathologic type predominates, but also other types and transitions between them. These features add to the evidence for a stem cell model, implying that neoplastic growth is linked to an increase in the resistance of aberrant stem cells and their progeny.

**Concepts of Salivary Gland Tumor Histogenesis**

1. Theory of basal reserve cells: Basal cells of both excretory and intercalated ducts are responsible for functional unit differentiation.

2. Theory of the pluripotent unicellular reserve cell: The excretory duct’s basal cells are responsible for the formation of all remaining salivary gland neoplastic transformation.

3. Theory of semipluripotent bicellular reserve cells: The excretory duct’s basal cells generate intercalated duct units, and the latter’s luminal progenitor cells are responsible for the production of intercalated, striated, and acinar units.

4. Multicellular theory: Cell division is possible in differentiated cells at all layers of the gland, including acinar and basal cells. Batsakis and colleagues hypothesised that excretory duct reserve cells cause malignancies like Mucoepidermoid carcinoma and Squamous cell carcinoma, while intercalated duct reserve (luminal) cells cause pleomorphic, monomorphic adenoma, Adenoid cystic carcinoma, and Acinic cell carcinoma.

The myoepithelial cell, according to Hubner and his colleagues, is responsible for the tumor’s morphologic diversity, including the formation of fibrous, mucinous, chondroid, and osseous areas.

According to Regezi and Batsakis, the intercalated duct reserve cell can differentiate into duct and myoepithelial cells, which can thereafter undergo mesenchymal metaplasia.²

**CONCLUSION**

Understanding the insight of histogenesis of salivary gland will help to set criteria for classification of tumors based on cell of origin and the morphological patterns.

**REFERENCES**


