

Histogenetic and Morphogenetic Concepts of Salivary Gland Neoplasms

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Abstract: *Salivary gland neoplasms have always been an field of interest for head neck and tumors because of its diversity in histogenesis and morphogenesis. Its of keen interest that all benign tumors arise from major salivary glands whereas on the other side all malignant arise from minor salivary glands. Reason for the above criteria can be understood only when a complete knowledge and understanding of the histogenesis of these tumors are known, so this paper emphasize on its histogenesis and morphogenesis of salivary gland tumors.*

Keywords: salivary gland tumors, morphology, histology

1. Introduction

Salivary gland tumours are a morphologically and clinically diverse group of neoplasms, which may present considerable diagnostic and management challenges to the pathologist or surgeon. Salivary gland tumours are rare with an overall incidence in the Western world of about 2.5–3.0 per 100 000 per year.

About 80% of all lesions are benign, hence salivary malignancies are particularly rare, comprising less than 0.5% of all malignancies and about 5% of cancers of the head and neck. When one considers that there are almost 40 named epithelial tumours in the latest World Health Organization (WHO) classification it is evident that some tumours are very rare indeed. Because of their rarity, individual clinicians are only infrequently required to manage these lesions and most cancers are managed in specialist centres⁽¹⁾. This, coupled with the degree of morphological diversity, makes this group of lesions one of the most interesting and challenging in the head and neck. Hence it is essential to highlight some current areas of difficulty or controversy among the epithelial tumours of the salivary glands.

The salivary glands have the most histologically heterogeneous group of tumours and the greatest diversity of morphological features among their cells and tissues. The classification of the salivary glands relies on the patterns of differentiation that reflect the organisation and cell types of the tissue. The histogenesis and morphogenesis of the salivary gland tumours with their many morphologic subtypes and myriad of histologic growth patterns is considered to be one of the important criteria to determine the pathogenesis of the tumours⁽²⁾.

Hence there is a need to investigate the various developmental processes, the cell types and various forms of differentiation involved in the salivary gland tumours to produce improved criteria for the segregation of individual types of tumours.

2. Definitions

- **Histogenesis:** Cell of origin for a neoplasm rather than the developmental process underlying the tumour.

- **Morphogenesis:** The process of differentiation inherent in the neoplasms and the resulting histopathology characteristic for that particular tumour.

3. Histogenetic Perspectives

Central to the histogenetic concepts is the determination of the types of cells in the normal salivary gland which are involved in the induction of the various neoplasms. Certain reserve cells in the normal adult salivary gland are replicating population which are ultimately responsible for the tumour formation. According to Gould, the process of cellular differentiation is more important in determining the histologic growth patterns used to classify the tumours than the exact cell responsible for a specific tumour arising from that organ.

Hence in an organ like the salivary gland with a wide range of differentiated cell types, it is possible that any one type of normal cell may give rise to morphologically distinct types of tumours. The underlying types of tumour cells, the synthetic mechanisms and the resulting organisation of these features in certain classes of salivary glands make it essential to distinguish between the two possibilities. It is on this basis that it is of interest to localise the so-called reserve cell (stem cells), or the differentiated cells with the capacity to divide, within the salivary gland and only then speculate on the pathways potentially capable of determining tumour morphology⁽⁴⁾.

3.1 Concepts of salivary gland tumour histogenesis⁽⁵⁾:

Basal reserve cell theory:

- Basal cells of both excretory and intercalated duct responsible for differentiation of the functional units.

Pluripotent unicellular reserve cell theory:

- Basal cells of excretory duct responsible for development of all remaining salivary gland units

Semipluripotent bi-cellular reserve cell theory:

- Basal cells of the excretory duct form the intercalated duct unit, and luminal progenitor cells of the latter are then responsible for development of intercalated, striated and acinar units

Multicellular Theory

- Differentiated cells at all levels of the gland, including acinar and basal cells, are capable of cell division.
- Of the aforementioned theories, the one that continues to have an impact on modern principles of tumour induction in these glands is the Semipluripotent bi-cellular reserve cell theory, put forth by Eversole in 1971.

3.2 Reserve Cell Hypothesis for Salivary Gland Tumors

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 downgrowths of bilayered ducts, and it was assumed that the inner or luminal layer derived from the outer or basal layer. As a result of these observations, the basal cells were considered reserve cells based on the premise that they functioned as stem cells, particularly for generation of duct luminal and acinar cells. With development and maturation of salivary glands, it was suggested, that such cells remained confined to the basal cell layer of excretory ducts. In this location, reserve cells associated with the excretory duct were presumed to be responsible for replacement of excretory duct luminal and basal cells and the progenitor cells for the intercalated duct.

The latter were then responsible for the development and replenishment of intercalated ducts, striated ducts, and acinar cells; hence, this concept was labelled the semipluripotential bicellular theory by Eversole, 1971. When originally proposed, the lack of specific evidence for this concept was emphasized. In 1977, the reserve cell concept was adopted and promoted as the underlying mechanism for the histogenesis of salivary gland tumors by Regezi and Batsakis. Although pleomorphic adenoma was originally linked to the excretory duct reserve cell by Eversole (1971) without explanation or apparent rationale, the intercalated duct reserve cell are now the histogenetic source for this tumor in the modification proposed by Regezi and Batsakis.

Differentiated cell types in mature salivary glands were initially suggested to be incapable of undergoing neoplastic alteration, and acinar and striated duct maintenance was achieved by a low level of mitotic activity of these fully mature or "end-differentiated" cells. The role of repair and replenishment could be assumed only by uncommitted stem (reserve) cells, and by inference, such cells were solely at risk for neoplastic induction.

Oncogenesis presumably occurred 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. Yet the necessity for salivary gland regeneration occurs infrequently.

Tumorigenic factors are likely to superimpose on gland cells undergoing physiological replacement. In this case, identification of normally cycling cells is more essential than elucidating potential stem cells.

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

Two central dogmas of current histogenetic classification schemes need to be evaluated critically.

- First, tumor induction is assumed not to occur in acinar cells, which are considered to be terminally differentiated and therefore incapable of further cell division.
- Second, dedifferentiation, whereby fully differentiated cells lose their functional characteristics, and transdifferentiation, whereby a fully differentiated cell can alter its functional characteristics to those of another differentiated cell phenotype, are both considered impossible.

However, based on available scientific data, dedifferentiation of normal tissues simply means a loss of specialized features, and in the salivary gland such alterations can occur both in vitro and in vivo. Similarly, cells in the salivary gland can undergo squamous and ciliated cell metaplasia. Many studies also state that acinar cells are in fact the main proliferating cell in the developing, maturing, regenerating, and mature parotid gland.

3.3 Muticellular histogenetic concept based on the Proliferative capacity of salivary glands:

Although the acini and the associated intercalated duct have an embryologic origin from simple ductal structures, there may be additional mechanisms of self renewal and regeneration in the mature gland in comparison with an immature gland. The salivary glands have only limited regenerative capacity but any insult to the salivary gland in the form of infection or inflammation may result in metaplastic alterations of the duct epithelium along with proliferation of the myoepithelial/basal cells. Any cell capable of replicating its DNA has a potential to express genes associated with neoplastic alteration, hence it is essential to catalogue the cell types of salivary gland that retain their capacity to divide.

All the cells of the salivary gland at all levels of the ductal system and lumen including the acinar, intercalated and striated duct have shown presence of mitotic figures. Hence differentiated cells are also capable of metaplastic alterations in terms of tumour induction.

Hence if a histogenetic approach to classifying salivary gland tumours deserves consideration, then it must be based on a "multicellular concept" since acinar cells or striated duct cells are at as much as risk of neoplastic alteration as any other cell in these glands.

The need for a histogenetic concept may be unnecessary in the diagnosis of salivary gland neoplasms as the pathologists are unable to determine a cell of origin for each tumour based on histologic features.

3.4 Histogenetic Theories and Interpretation of Tumor Immunohistochemistry

Undue emphasis on histogenetic concepts to explain immunohistochemical results in salivary gland tumors can also lead to false conclusions. Immunostaining for S-100 protein is done to detect myoepithelial cell participation in tumors. In the normal salivary gland, myoepithelium is found to be positive for S-100 protein, and because antibodies to S-100 protein generally stain the modified myoepithelial cell, that is, nonluminal tumor cell, of pleomorphic adenomas and other salivary gland tumors. Hence it was assumed to imply a key histogenetic role for myoepithelial cells in salivary gland tumors. In fact, various subunits of S-100 protein localize to acini and/or ducts of salivary glands and not myoepithelial cells. The occasional crescentic-shaped structures associated with normal acini, which are positive for S-100 protein, are fine, terminal branches of unmyelinated nerves with which the gland is richly endowed⁽⁷⁾.

Adenoid cystic carcinomas of all subtypes have S-100 protein positive luminal cells and negative basal or modified myoepithelial cells. Assuming that S-100 protein is a lineage marker for myoepithelium leads to a misinterpretation that positively stained luminal tumor cells "might be closely related to true or modified myoepithelial cells". Such results indicate that whether antibodies to S-100 protein stain luminal or myoepithelial-like cells in salivary gland tumors, it is simply a reflection of genetic expression in neoplasia without necessarily implying a definite histogenetic role for a particular cell of the normal gland.

This is most apparent in pleomorphic adenoma, where the outer layers of two-tiered epithelial cells show no or variable degrees of staining for S-100 protein, both within and between individual cases. The data, then, do not support the contention that myoepithelial cells are the direct precursors of certain salivary gland tumors.

4. Patterns of Differentiation in Salivary Gland Neoplasms

Factors which determine the histologic pattern of the tumour that is central to the categorisation of the salivary gland tumours are:

- The tumour cell organisation
- The tumour cell type or types of differentiation
- The materials synthesised by the cells
- Their placement within the tumour

These factors are independent but highly intergrated and operate between various types of salivary gland tumours or within one type.

The bicellular constitution of the salivary gland tumours composed of luminal and neoplastically modified myoepithelial cells was put forth by Batsakis. Such tumours include: Pleomorphic adenoma, adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, terminal duct carcinoma, monomorphic adenomas of certain types, acinic cell

carcinoma, muco-epidermoid carcinoma and Warthin's tumour.

The neoplastic myoepithelial cell is capable of differentiating into a variety of cytologic forms and a wide range of structural modifications namely spindle, plasmacytoid, epithelial and clear cells.

The form, number and distribution of luminal epithelial cells are also variable. Along with these, the ratio of the ductoid or gland-like structures to the myoepithelial cells is a major reason for the wide histological spectrum in a single salivary gland tumour.

The deposition of certain extracellular secretory products by the neoplastic myoepithelial cells is also a characteristic feature of salivary gland tumours which may also differ in the various types. They account for the myxoid stroma of pleomorphic adenoma and the pseudoluminal (cystic) spaces in adenoid cystic carcinoma. The secretory products are often composed of basal lamina (excess amounts), elastic and collagen fibres and glycosaminoglycans. Thus the highly controlled developmental process helps in the classification as well as explain:

- The diversity of histologic features within the classes of tumours
- The overlap of histologic features between the various sub-types
- The formation of multiple growth patterns which may be characteristic of another tumour with a different biological behaviour.

5. Morphogenetic Concepts

There are basic structural patterns in the developing and mature salivary gland which may be reflected in the salivary gland tumours and in the various differentiation patterns within the groups of tumours. The morphogenetic approach focuses on tumour differentiation and other cellular processes that critically influence the histomorphology. They are unconcerned with the tumour initiation processes even though these are of primary importance and are likely to influence many aspects of tumour development. Morphogenetic processes determine the specific features allowing recognition of each normal organ or tissue as well as differentiation of salivary gland tumours.

The importance of this concept is that it relates the histology of the neoplastic processes directly to the classification of the salivary gland tumours rather than designating a specific cell of origin that are generally impossible to precisely identify once the tumour is clinically overt, thus having better practical applications compared to the histogenetic concepts.

Through an understanding of the ducto-acinar concept it is possible to appreciate the evolution of histological features in salivary gland tumours, which is essential for proper morphological classification. Rather than emphasize the resemblance of particular salivary gland tumours 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 as defined in current classifications. Evaluation of tumors on the basis of 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.

Using the normal salivary gland ducto-acinar unit with its combination of duct luminal or acinar cells bordered externally by a row of myoepithelial and/or basal cells as a model, salivary gland tumors can be divided effectively into two broad categories: one a caricature of the normal gland with two basic cell types, that is, neoplastic luminal and myoepithelial or basal cells, and the other differentiating either neoplastic luminal cells or myoepithelial and/or basal cells. 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 cells. On this basis, as illustrated in a simplified fashion, three primary histological patterns evolve in salivary gland tumors.

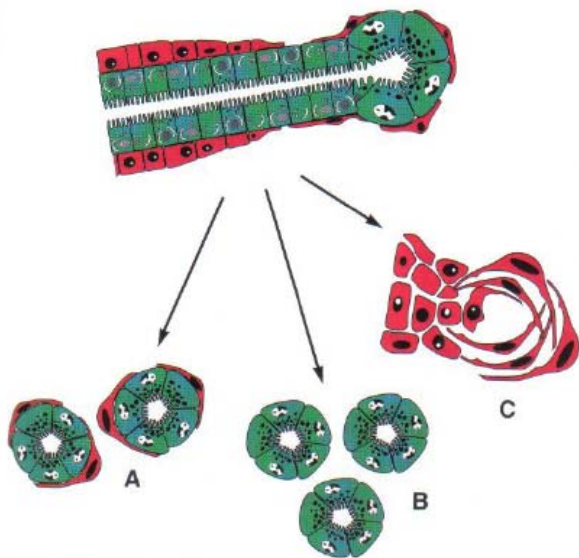


Figure 1: Salivary ducto-acinar unit showing potential for differentiation of three salivary gland tumour pathways

- Tumours arising from combination of ductal/luminal and/or acinar cells along with outer layer of myoepithelial/basal cells.
- Tumours largely composed of luminal cells which may reveal differentiation into non-specific ductal, acinar or goblet cells and/or combination of these cells.
- Tumours almost entirely formed by myoepithelial/basal 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 useful in describing these tumors for classification purposes. Accumulated basal lamina and glycosaminoglycans may be present in certain bicellular 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 influence the final morphology of a particular salivary gland tumor class.

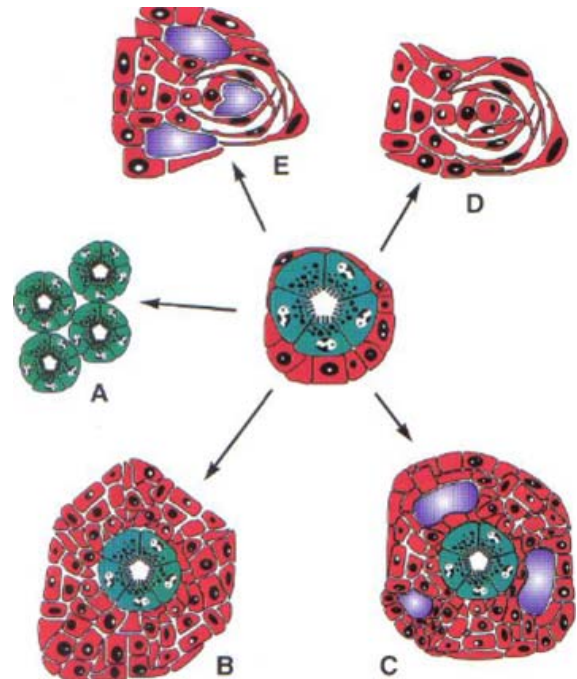
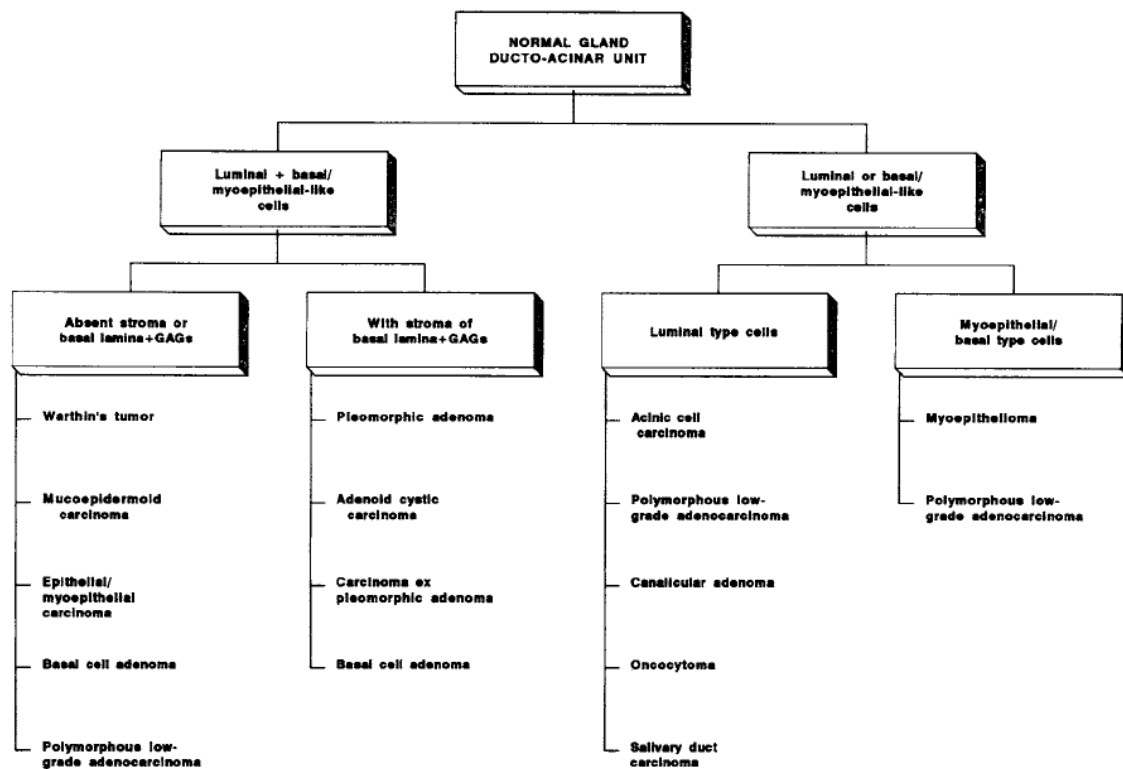


Figure 2: Cross-section of the ducto-acinar unit with the central luminal (luminal/acinar) and surrounding non-luminal cells (myoepithelial and basal cells) which can be used to show further differentiation of the salivary gland tumours when coupled with excess synthesis of basal lamina and GAGs.

- Exclusive proliferation of luminal cells which may vary in type
- Bidirectional differentiation without extracellular matrix materials
- Proliferation of both luminal and non-luminal cells with histologically evident foci of extracellular matrix materials
- Myoepithelial or basal cell proliferation without extracellular matrix materials
- Myoepithelial or basal cell proliferation with extracellular matrix materials

Using cytological differentiation and the proportion of luminal to nonluminal tumor cells as additional morphological criteria fully accounts for the final histology of salivary gland tumors as well as their formidable histopathological spectrum. Based on an increasing literature relative to systematic and comparative studies of salivary gland tumors, it is possible to derive a rather simple taxonomic form of flow diagram that could serve as a basis for defining diagnostic criteria for the complex array of neoplasms originating in these glands).



-Neoplasms composed of undifferentiated cells- Undifferentiated carcinoma, small cell carcinoma

Figure 3: Potential interrelationship between salivary gland tumors within the various taxonomic categories

Although the majority of salivary gland tumor subtypes are considered separate entities on the basis of their distinctive histology, many are interrelated. Awareness of this interrelationship helps to explain the overlap in histologies between some subtypes and the differential diagnostic and classification problems that all too frequently arise, as well as the particularly broad spectrum of histology within any individual subtype that itself poses diagnostic problems for the pathologist.

The cell types differentiating in salivary gland tumors, their organizational structure and the effects on tumor morphology of the extracellular matrix and basal lamina synthesized by the myoepithelial/ basal cells assists in appreciating how these factors influence the final histology. The knowledge of cellular differentiation, architectural organization, and synthetic products even within the subtypes of salivary gland tumors allows us to establish more tightly defined classification criteria.

5.1 Genetics in salivary gland neoplasms:

The goal of the molecular biological studies of salivary gland tumours is to define objective markers that may supplant the subjective phenotypic evaluation in the diagnosis, biological assessment and therapeutic stratification of patients with these tumours. The following molecular genetic events tentatively characterize some of these tumours:

- 1) Chromosomes 3p21, 8q12 and 12q13-15 rearrangements and the PLAG-1 and HMGI-C genes in pleomorphic adenomas
- 2) Translocations of chromosomes 11q21 and 19p13 in both Warthin tumour and mucoepidermoid carcinoma.

- 3) Structural and molecular alterations at 6q, 8q, 12q in adenoid cystic and carcinoma ex-pleomorphic adenoma.
- 4) Elevated HER-2 gene expression and gene amplification in mucoepidermoid, salivary duct and adenocarcinomas.

Oncogenes:

Oncogenes may be defined as genes whose function becomes enhanced in carcinogenesis, which usually play a role in controlling cell proliferation and which commonly encode growth factors and their receptors, transcription factors, signal transducers and apoptosis regulators. The complex mechanisms of tumor induction and progression in salivary gland tumors are likely to be best illustrated by investigating the chromosomal aberrations and oncogene expression.

EGFR

Several studies have shown high expression of EGFR/HER-2/neu family members in mucoepidermoid and adenoid cystic carcinoma. The data suggest a biological role for members of this pathway in these tumours and their potential use as a target for therapy.

C-erbB-2/HER-2/neu

This is an oncogene that encodes for a transmembrane glycoprotein receptor involved in cell growth and differentiation. The gene is a member of the EGFR signal transduction family and has been shown to be overexpressed in aggressive breast cancer. Studies in salivary gland adenocarcinoma, including salivary duct and mucoepidermoid carcinoma, point to a general consensus on the association of HER-2 overexpression and adverse clinicopathologic features.

C-Kit

This is a proto-oncogene that encodes a transmembrane receptor type tyrosine kinase that belongs to the colony-stimulating factor-1 (CSF-1) and platelet-derived growth factors (PDGF;4-6). Upon binding to its ligand, a signalling cascade is initiated to stimulate growth and differentiation of haematopoietic cells. Studies of C-kit in salivary gland tumours have largely focused on adenoid cystic carcinoma and findings vary considerably. C-kit expression appears to be restricted to adenoid cystic carcinoma and myoepithelial carcinomas but absent in polymorphous low-grade adenocarcinoma and other types of salivary gland tumours.

None of the highly expressed tumours manifested genetic mutations at exons 11 & 17 which underscore that a mechanism for gene activation and other genetic alterations may play a role. A more recent study of this gene indicates high expression in other types of salivary gland neoplasms as well. (adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma and monomorphic types of adenoma).

PLAG1

The pleomorphic adenoma gene 1 (PLAG1) encodes a zinc finger protein, which recognizes a specific bipartite DNA consensus sequence and acts on a wide range of target genes. Most significantly upregulated by PLAG1 are growth factors such as insulin-like growth factors IGF-II and IGF-IR. The most frequent chromosomal translocation to occur in human salivary gland pleomorphic adenomas (PAs) is t(3;8)(p21;q12). This involves 'promoter swapping', whereby the CTNNB1 promoter from the CTNNB1 gene (which codes for the ubiquitously present β -catenin protein involved in cell-to-cell adhesion and Wg/Wnt signalling pathway) is used to drive the PLAG1 gene. Similarly, in the t(5;8)(p13;q12) translocation, the leukaemia inhibitory factor receptor takes on the role of promoter.

A number of studies have shown down-regulation of Wnt inhibitory factor 1 (WIF1), an inhibitor of the Wnt signalling pathway with an expected up-regulation of β -catenin. The Wnt signalling pathway essentially leads to an increase in free β -catenin and translocation of this to the nucleus, to regulate expression of target genes. There is some evidence to suggest that PLAG1 may bypass the Wnt pathway to directly activate binding sites in the β -catenin promoter region.

Mect1-Maml2 fusion oncogene

Tonon *et al* in 2003 first described a novel fusion product from a t(11;19)(q21;p13) chromosomal translocation that disrupted the Notch signalling pathway and could be implicated in salivary gland tumourigenesis. The intracellular domain of the Notch protein regulates gene expression in the nucleus via activation of the transcription factor, CBF1/*suppressor of hairless/Lag-1* (CSL).

The t(11;19)(q14-21;p12-13) chromosomal translocation is characteristic of mucoepidermoid carcinomas (MECs) of the salivary glands, which fuses exon1 from the mucoepidermoid carcinoma translocated 1 (MECT1) gene with exons 2-5 of the Mastermind-like gene family member, MAML2. Studies have consistently shown the association of the MECT1-MAML2 fusion transcript with MECs, but its

absence in Warthin's tumour, polymorphous low-grade adenocarcinoma and acinic cell carcinomas makes detection of the fusion gene of diagnostic value.

HMGIC/HMGA2 fusion oncogenes

Around 12% of PAs display chromosomal aberrations involving the 12q13-15 segment, which was shown to code for HMGIC or HMGA2. HMGIC is a member of the high mobility group (HMG) gene family that codes for non-histone components of chromatin and, therefore, has a role in transcription regulation. A number of fusion partners have been demonstrated to alter expression of HMGIC, most notably FHIT and NFIB. Analysis has shown that certain exons of HMGIC are expressed more than others in tumours with activation of the gene, further stressing that rearrangements and fusions are key to overexpression, which may be implicated in malignant transformation to carcinoma ex PA (CXPA).

ras

RAS is a G protein or GTPase that oscillates between activated (RAS-GTP) and inactivated states (RAS-GDP) in response to a variety of ligands, including epidermal growth factor receptor and interleukin 2 (IL-2). There are three human *ras* genes, *H-Ras*, *N-Ras* and *K-Ras*, with the latter having two splicing variants, *K-Ras4A* and *K-Ras4B*. Inactivation of RAS is accelerated by GTPase-activating proteins (GAPs) and increased release of bound GDP triggered by guanine nucleotide release proteins.

Mutations of *H-Ras* have been shown in 35% of salivary gland PAs, 23% of adenocarcinomas and 45% of MECs. A number of specific mutations have been identified, including a missense mutation at codon 61 of the *H-Ras* gene, identified as bypassing normal growth factor-dependent *ras* signalling, and transversion mutations at codons 12 and 13.

c-fos

The product of the *c-fos* oncogene is a transcription factor up-regulated in response to ligands such as epidermal growth factor, which dimerizes with *c-jun* to act as transcription factor AP-1 that binds to the TPA-response element in a variety of genes concerned with growth and cellular differentiation.

It was shown that lower degrees of staining with the *c-fos* oncogene correlated very strongly with poorer cellular differentiation across a broad spectrum of salivary gland tumour types. In the poorly differentiated adenocarcinoma group, for instance, 96.8% of tumour specimens were associated with paucity of staining.

Whereas *c-fos* has been found to be overexpressed in osteosarcomas, its underexpression in poorly differentiated salivary gland tumours relative to normal salivary gland tissue is a reflection of its role in inducing cellular differentiation.

Sox-4

Sry-related HMG box 4 (*Sox4*) is a transcription factor which has been implicated in tumourigenesis, possibly via actions on Wnt pathway signalling or via up-regulation of src tyrosine kinases, such as p56^{lck}. The most significantly

overexpressed oncogene in ACCs relative to normal salivary gland was *Sox4*. **A summary of the oncogenes mentioned throughout the text, their role in salivary gland tumorigenesis (Table 1)**

<i>Oncogene</i>	<i>Salivary gland tumour</i>
<i>Mam12</i>	MEC, Warthin's tumour
<i>c-kit/CD117</i>	ACC, lymphoepithelioma-like carcinoma, myoepithelial carcinoma
<i>HER2/neu</i>	SDC, ACC, MEC, CXPA
<i>H-ras</i>	Pleomorphic adenoma, adenocarcinomas, MEC, CXPA
<i>PLAG1</i>	Pleomorphic adenoma, CXPA
<i>WNT1</i>	Pleomorphic adenoma, CXPA, ACC, MEC epithelial-myoeplithelial carcinoma
<i>HMGIC/HMGA2</i>	Pleomorphic adenoma
<i>Mdm2</i>	Pleomorphic adenoma, myoepithelial carcinoma, ACC, CXPA
<i>c-fos</i>	Underexpression correlates with poorer differentiation in a wide variety of tumour types
<i>Sox4</i>	ACC

Tumour suppressor genes

TP53

TP53 is a tumour suppressor gene located at the short arm of chromosome 17. The protein product acts as a transcription factor for cell differentiation, proliferation and death. The role of this gene in salivary gland tumorigenesis remains unknown. Studies of different tumours have yielded variable results. The incidence of p53 expression in other benign, malignant and hybrid tumours is low and does not correlate with recurrence. At present there is insufficient information on the correlation between p53 and outcome⁽⁶⁾.

6. Summary

Histogenetic terminology is an integral part of the classification of human tumors. Evidence, however, that in each case a particular tumor type arises from a cell within the tissue specified by the diagnostic terminology is lacking. Much of the evidence shows that all parts of salivary gland parenchyma, whether acinar or duct-and both luminal and basal-cells, can proliferate under a variety of circumstances and, therefore, cannot be excluded as potential cellular sites for neoplastic induction. Hence histogenetic concepts offer little advantage to the diagnostician.

Origin from the many cell forms composing salivary glands does not necessarily imply that the resulting histopathology and cellular differentiation of the tumor will reflect the parent cell, however, or even guarantee a consistent tumor morphology. In fact, the plasticity of the normal salivary gland for cellular alterations at all levels under various experimental and nonneoplastic conditions suggests the contrary. 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. However, there is mounting direct evidence that cell renewal can result from

duct luminal and acinar cells that rapidly re-enter the cycling cell pool. Frequently cycling cells are generally considered the more obvious target for neoplastic transformation. 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; acinar cells, as they form the bulk of the gland parenchyma, present the greatest proportion of cycling cells in rat and human salivary glands.

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, 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.

Perhaps in the salivary gland, oncogenetic events that follow initiation of the multistage process that results in neoplastic transformation are partially governed by the type of cell in which neoplastic transformation has occurred, influencing both the biology of the tumor and the pattern of cellular differentiation within it.

Further research is necessary to obtain reliable information regarding the histogenesis and morphogenesis of salivary gland tumors and thus allow study of the processes that govern the final histological characteristics of the tumor, as well as the exact relationships between the various subtypes of salivary gland tumors. Such research will eventually improve the lot of pathologists burdened with the problems involved in classifying these challenging human neoplasms.

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