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Molecular Pathology and Biomarkers

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Abstract

The field of salivary gland tumor biology is quite broad, given the numerous subtypes of both benign and malignant tumors originating from the major and minor salivary glands. Knowledge about the molecular pathology of these lesions is still limited, and there are few clinically useful diagnostic and prognostic biomarkers. However, recent discoveries of certain key genomic alterations, such as chromosome translocations, copy number alterations, and mutations, provide new insights into the molecular pathogenesis of these lesions and may help to better define them. It is also hoped that this new knowledge can help to guide therapy, but this translation has been somewhat slow to develop, perhaps due to the rarity of these tumors and the lack of large, randomized studies. However, because of the limitations inherent in what surgery and radiation can provide, there is an urgent need for understanding of the mechanisms of carcinogenesis in these tumors individually, so that chemotherapy and/or targeted therapy can be rationally selected.

Introduction

For the majority of salivary gland tumors, the etiology remains unknown, with presumably sporadic alterations leading to tumor formation. There are no hereditary syndromes associated with salivary gland neoplasms other than the recently suggested association between germline *BRCA* mutations and salivary gland cancer [1]. Nor are these lesions exposure related, besides the relationship between the benign Warthin tumor and smoking. As such, research into these tumors has not had the benefit of such occurrences that often help to point to critical events in tumorigenesis.

The purpose of this chapter is to focus on the tumor types for which we have significant knowledge of the molecular alterations. Interestingly, there are unique molecularly defining events for many of these tumor types (table 1). Each tumor subtype is reviewed, and what is known about their molecular underpinnings that currently helps to define their characteristics is presented.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common of the salivary gland malignancies ($\approx 34\%$ of carcinomas [2]) and is thought to arise from stem/progenitor cells in excretory ducts. Its clinical behavior is known to be dependent on the histology [3]. Tumors with a predominant epithelial/solid component are considered high-grade, whereas those with a predominant cystic/mucoid component are low-grade. The high-grade tumors are known to behave quite aggressively, with a high likelihood of regional and distant metastases, whereas the low-grade tumors are quite indolent in their course.

MECs are characterized by a unique t(11; 19) (q21–22;p13) translocation, resulting in a fusion of the two transcriptional coactivators mastermind-like 2 (MAML2) and cyclic AMP (cAMP) response element-binding protein (CREB)-regulated transcription coactivator 1 (CRTC1) [4, 5]. The *CRTC1-MAML2* fusion gene encodes a chimeric protein in which the Notch-binding domain of MAML2 is replaced by the CREB-binding domain of CRTC1, or more rarely CRTC3, fused to the transactivation domain of MAML2. The fusion protein activates transcription of cAMP/CREB target genes, including, for example, the epidermal growth factor receptor (EGFR) ligand amphiregulin, leading to activation of EGFR signaling and increased growth and survival of MEC cells [6]. Interestingly, recent studies have suggested that CRTC1-MAML2-positive MEC cells are highly sensitive to inhibition of EGFR signaling in a xenograft model, suggesting that targeting this pathway may offer a new approach to systemic treatment of patients with advanced, unresectable fusion-positive MECs [6].

Recent studies have convincingly demonstrated that the *CRTC1-MAML2* fusion is a specific and clinically useful biomarker preferentially found in low- and intermediate-grade MECs with a favorable prognosis [7–9]. The fusion may occasionally also be found in high-grade MECs with a poor prognosis, and in these cases, it is often in combination with loss of the *CDKN2A* tumor suppressor gene [10]. However, most high-grade MECs are fusion-negative, indicating that they may represent misclassification of high-grade MEC-like adenocarcinomas (not otherwise specified). A recent genome-wide array comparative genomic hybridization study suggested that MECs may be subclassified into (i) fusion-positive, low- and intermediate-grade MECs with no or few genomic imbalances and a favorable prognosis; (ii) fusion-positive, high-grade MECs, often with *CDKN2A* deletions, multiple genomic imbalances, and a poor prognosis, and (iii) fusion-negative, high-grade MEC-like adenocarcinomas with multiple genomic imbalances and a poor prognosis [8]. Interestingly, previous studies have shown that a subset of the latter tumors has a t(6; 22) (p21;q12) translocation, resulting in an *EWSR1-POU5F1* gene fusion [11]. Taken together, these studies show that the spectrum of MEC-like tumors is broad and heterogeneous both histologically and genetically.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) arises from stem/progenitor cells in intercalated ducts and may have quite a varied clinical course. It is the second most common salivary gland carcinoma, constituting approximately 22% of malignant salivary tumors [2]. While these

tumors have a generally slow growth rate, they do have a poor long-term prognosis, with a high propensity for perineural invasion and distant metastases. There is currently no effective treatment available for patients with advanced recurrent and/or metastatic disease.

ACC is characterized by a t(6; 9)(q22–23;p23–24) chromosomal translocation, resulting in a fusion involving the *MYB* oncogene and the transcription factor gene *NFIB* [12]. The *MYB-NFIB*-encoded fusion oncoprotein activates transcription of *MYB* targets of key importance for oncogenic transformation [9]. *MYB* activation due to gene fusion or other mechanisms is found in more than 80% of head and neck ACCs and is a novel diagnostic biomarker for this disease [9, 13, 14]. There is currently no evidence to suggest that the fusion has prognostic significance. However, since *MYB* is an oncogenic driver in ACC, it is also a potential therapeutic target. At present, it is not known whether *MYB*-negative ACCs are true ACCs or whether they represent a subset of tumors with an ACC-like morphology, such as, for example, polymorphous low-grade adenocarcinoma (PLGA) or basal cell adenocarcinoma.

Genomic profiling studies have shown that ACC generally has a rather quiet genome, with few copy number alterations compared to other high-grade carcinomas, consistent with the notion that the *MYB-NFIB* fusion is the major oncogenic event in ACC [12, 15]. Deletions involving 12q, 6q, 9p, 11q, 14q, 1p, and 5q and gains involving 1q and 22q are most common. Losses of 1p, 6q, and 15q are specifically associated with high-grade tumors, whereas loss of 14q is exclusively seen in grade I tumors. There is now clear evidence to suggest that deletion of 1p36.33-p35.3 is a biomarker associated with high-grade tumors with a poor prognosis [12, 16].

Using next-generation sequencing, the complete exomes of more than 80 ACCs have been sequenced. Stephens et al. [17] reported a relatively low average mutational rate of 13 per sample, with a range of 2–35 mutations per sample. The most common mutations were in *NOTCH1/2* (3/24 cases), *SPEN* (5/24 cases), and *FGF2* (3/24 cases). There was additionally a cluster of mutations found in genes involved in histone modification and chromatin remodeling. Similar findings of a low mutational rate (22 somatic mutations per sample on average, with a range of 1–36) were also identified by Ho et al. [15], along with similar identification of mutations in chromatin-regulating genes in 35% of cases. Additionally, there were mutations within the *FGF/PI3* kinase pathway in 30% of samples as well as in the *NOTCH1* pathway in 13% of the cases.

A third sequencing study was performed in a cohort of patients with recurrent and metastatic ACCs, looking specifically at cancer-related genes [18]. Alterations that could be targeted by specific therapies were evaluated; 44 actionable alterations were found in the cohort of 28 tumors, and 12/28 (43%) of patients had at least one mutation. Therefore, it was postulated that the use of DNA sequencing can help to guide therapy in those patients who otherwise may have no other known treatment option. Taken together, the results demonstrate that the mutational rate of any one particular gene in ACC is quite low, suggesting that, apart from the *MYB-NFIB* gene fusion, there are numerous alterations that likely must occur for the cancer to arise.

KIT is a tyrosine kinase thought to have oncogenic effects with many possible downstream targets that promote growth. There appears to be a predominance of expression in the solid variant of ACC [19], and an overwhelming number of studies has identified overexpression in 78–100% of cases [20–27]. Mutations in *KIT* in ACC are very rare [15, 17].

EGFR is a known oncogene that encodes a cell surface protein with positive growth effects upon heterodimerization. In other tumor types, such as head and neck squamous cell carcinoma, there are known activating mutations in exons 19 and 21, with oncogenic effects. In ACC, there appears to be overexpression in up to 75–85% of tumors [28], but the presence of these mutations is rare [29]. Furthermore, overexpression is believed to not be associated with gene amplification [30].

Salivary Duct Carcinoma

Salivary duct carcinoma (SDC) is an aggressive cancer with a high risk of regional and distant metastases and a 5-year overall survival of 43% [31]. Interestingly, it has a similar or identical histological appearance to that found in invasive ductal breast cancer. Thus, this carcinoma shows frequent *HER2 (ERBB2)* overexpression, occurring in >80% of tumors [32, 33] along with gene amplification [34], though it is not believed to be a predictor of survival [23]. The androgen receptor has also been identified to be highly expressed in SDC [35], but not due to gene amplification [14]. EGFR has also been found to be overexpressed in at least half of SDCs [36], although it remains to be seen whether this is a viable therapeutic target. Mutations in *PIK3CA* have been identified in 20–24% of SDCs [37], suggesting that this pathway could be a potential target for therapy.

Mammary Analog Secretory Carcinoma

Mammary analog secretory carcinoma (MASC) is a relatively newly described salivary gland malignancy that predominantly affects the parotid gland [38]. This carcinoma was initially confused with acinic cell carcinoma, low-grade cystadenocarcinoma, or MEC, but the presence of a t(12; 15)(p13;q25) translocation and *ETV6-NTRK3* gene fusion, analogous to secretory carcinoma of the breast, identified MASC as a distinct entity [38–40]. The *ETV6-NTRK3* fusion is a hallmark of MASC [41]. The clinical behavior of MASC appears to be similar to that of acinic cell carcinoma, wherein it can behave aggressively at times but typically has a relatively indolent course [40, 41].

Pleomorphic Adenoma

Pleomorphic adenoma (PA) is the most common subtype of salivary gland neoplasm. It is a benign tumor that, if treated adequately, has an excellent prognosis. Histologically, PAs show a pronounced morphological diversity, with epithelial and myoepithelial cells forming a variety of patterns in an often fibrous, myxoid or condroid stroma. PA was the first benign human tumor that was shown to be characterized by tumor type-specific chromosomal translocations [42]. Subsequent studies revealed that PAs are frequently characterized by recurrent translocations preferentially affecting 8q12 (>50%) and 12q14–q15 (≈ 15%) [43]. These rearrangements result in gene fusions affecting the transcription factor genes *PLAG1*

and *HMGA2* (table 1) [43]. These fusions have not been encountered in any other type of salivary gland tumor and may therefore be useful as biomarkers to differentiate PA from its mimics, including, for example, ACC and PLGA. Previous studies have also indicated that PAs with *PLAG1* gene fusions often have activation of HRAS [44]. Gene amplifications and overexpression of genes in 12q13–q15, including *HMGA2*, *MDM2*, *CDK4*, *TSPAN31*, and *GLI1*, are found in a subset of PAs [45]. *TP53* mutations are infrequent in PA but are common in carcinoma ex-PA (CXPA) [45].

Carcinoma Ex-Pleomorphic Adenoma

CXPA is a carcinoma arising within a preexisting PA. CXPA constitutes approximately 12% of all salivary gland carcinomas. The malignant component is often an adenocarcinoma (not otherwise specified) or an undifferentiated carcinoma but may be any other histological subtype. CXPAs that are noninvasive or minimally invasive have an excellent prognosis, whereas invasive tumors are usually high-grade, aggressive lesions with a poor prognosis.

CXPAs are characterized by the genetic alterations that are typical of PAs: that is, translocations and gene fusions involving *PLAG1* and *HMGA2* (table 1). In addition, subsets of these tumors have amplifications of *HMGA2* and *MDM2* in 12q14–q15, mutations of *TP53*, and/or amplification of *HER2* as molecular biomarkers of malignant transformation [9, 45]. CXPAs with *HER2* amplification are mainly SDCs-ex-PAs. Interestingly, there are anecdotal reports showing that these patients may benefit from anti-HER2 treatment with trastuzumab [9]. Other alterations associated with adenoma-carcinoma progression are deletions involving 5q23.2–q31.2 and gain/amplification of the *PLAG1* and *MYC* oncogenes [45].

Hyalinizing Clear Cell Carcinoma

Hyalinizing clear cell carcinoma (HCCC) is a rare, low-grade minor salivary gland carcinoma characterized by clear cells growing in nests and cords in a hyalinized stroma [46]. The prognosis is excellent, with only occasional metastatic spread. HCCC shows histological overlap with other salivary neoplasms, such as myoepithelial carcinoma, epithelial-myoepithelial carcinoma, and MEC. Recent studies have demonstrated that HCCC is frequently characterized by a t(12; 22) (q13;q12) translocation, resulting in an *EWSR1-ATF1* gene fusion [46]. *EWSR1* gene rearrangements were recently also detected in clear cell variants of aggressive myoepithelial carcinomas as well as in clear cell odontogenic carcinomas [47, 48]. These findings, together with the original identification of *EWSR1-ATF1* fusions in soft tissue clear cell sarcomas [49], provide evidence for a unifying concept for several tumor types with clear cell morphology.

Polymorphous Low-Grade Adenocarcinoma and Cribriform Adenocarcinoma of Minor Salivary Glands

PLGA and cribriform adenocarcinoma of minor salivary glands (CAMSG) are low-grade carcinomas that mainly occur in the oral cavity and oropharynx, respectively. There is some controversy as to whether they are histogenetically separate entities or variants along one

spectrum. PLGAs were recently shown to have activating *PRKD1* hotspot mutations (p.Glu710Asp) in 73% of cases [50]. In contrast, *PRKD1* mutations were not detected in any other subtypes of salivary neoplasms analyzed (n = 299), indicating that *PRKD1* mutations define a subset of PLGA and may be used as a diagnostic biomarker to differentiate PLGA from other mimics. Moreover, *PRKD1* mutations were significantly associated with the metastasis-free survival of patients with malignant salivary gland tumors. Interestingly, classical CAMSG was recently shown to have rearrangements of *PRKD1*, *PRKD2* or *PRKD3* in 75% of the cases, including *ARID1A-PRKD1* and *DDX3X-PRKD1* gene fusions [51]. Taken together, these findings support the concept of a possible shared pathogenesis for PLGA and CAMSG.

Conclusion

It is evident that our knowledge of the molecular pathogenesis of salivary gland tumors is steadily growing, with the identification of novel unique molecular alterations in specific tumor types. It is hoped that further discoveries will lead to improved diagnosis, better prognostication, and additional treatment options for patients with these tumors.

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Table 1

Recurrent chromosome translocations and gene fusions in salivary gland neoplasms

Diagnosis	Chromosome translocation	Gene fusion	Comments
MEC	t(11;19)	<i>CRTC1-MAML2</i>	Found mainly in low- and intermediate-grade MECs
	t(11;15)	<i>CRTC3-MAML2</i>	
High-grade MEC-like tumors	t(6;15)	<i>EWSR1-POU5F1</i>	
ACC	t(6;9)	<i>MYB-NFIB</i>	Fusion-negative ACCs have <i>MYB</i> gene activation through other mechanisms
HCCC	t(12;22)	<i>EWSR1-ATF1</i>	
CXPA	t(8q12)	<i>PLAG1</i> fusions	Same fusions as in pleomorphic adenomas
	t(12q14–15)	<i>HMGA2</i> fusions	
MASC	t(11;15)	<i>ETV6-NTRK3</i>	<i>ETV6-NTRK3</i> is found also in secretory carcinomas of the breast as well as in certain pediatric neoplasms
CAMSG		<i>ARID1A-PRKD1</i> <i>DDX3X-PRKD1</i>	<i>PRKD1</i> is also mutated in polymorphous low-grade adenocarcinoma
PA	t(8q12)	<i>CTNNB1-PLAG1</i>	
		<i>FGFR1-PLAG1</i>	
		<i>TCEA1-PLAG1</i>	
		<i>CHCHD7-PLAG1</i>	
		<i>LIFR-PLAG1</i>	
	t(12q14–15)	<i>HMGA2-NFIB</i> <i>HMGA2-WIF1</i> <i>HMGA2-FHIT</i>	