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Genetic Alterations in Salivary Gland Cancers

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Abstract

Salivary gland cancers are an incredibly heterogeneous group of tumors that include 24 histologically distinct tumor types. The use of new genetic methods has paved the way for promising advancements in our understanding of the molecular biology underlying each type of tumor. The objective of this review was to highlight common oncogenes, tumor suppressor genes, and cytogenetic and epigenetic changes associated with the most common tumor types: mucoepidermoid carcinoma, adenoid cystic carcinoma, salivary duct carcinoma, mammary analogue secretory carcinoma, hyalinizing clear cell carcinoma, carcinoma ex pleomorphic adenoma, and acinic cell carcinoma. Recent insights into the pathogenesis of each cancer subtype have helped better define and classify these tumors. Further research in salivary gland cancers should focus on determining the key genes involved in the tumorigenesis of each distinct malignancy and identifying individualized chemotherapies directed at these targets.

Keywords

acinic cell carcinoma; adenoid cystic carcinoma; cytogenetics; epigenetics; genetics; hyalinizing clear cell carcinoma; mammary analogue secretory carcinoma; mucoepidermoid carcinoma; salivary duct carcinoma; salivary gland cancer

Introduction

Salivary gland malignancies are a heterogeneous group of tumors that currently involves 24 histologically distinct cancer subtypes.¹ Thus there is also significant heterogeneity in the aberrant genetic and molecular pathways that contribute to the development of each specific tumor. Systemic therapies for salivary gland cancers are reserved for advanced disease and have only achieved a modest response, with cisplatin-based regimens the most frequently studied.² However, the advent and the now widespread use of new genetic methods have paved the way for promising advancements in our understanding of the molecular biology underlying each type of tumor.

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The objective of this review was to present a broad current understanding of the genetic landscape that defines this heterogeneous group of tumors. We highlight the common cytogenetic and epigenetic changes associated with each type of salivary gland cancer as well as any oncogenes and tumor-suppressor genes (TSGs) that may play an important role in the pathogenesis of disease (Fig. 1). We hope that the information provided here will offer a solid foundation for the future exploration of more specific diagnostic tools and individualized, genetically targeted therapies.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy, accounting for 30% to 35% of all malignant neoplasms of the major and minor salivary glands.³⁻⁵ Histologically, it is mainly composed of mucous, epidermoid, and intermediate cell types that form cysts.^{6,7} Current grading systems are based on the extent of cyst formation, differentiation of the 3 main cell types, and cytomorphologic changes.⁸⁻¹¹ However, prognosis and treatment strategies based on these traditional grading systems can be controversial, and promising genetic and molecular markers can offer new outlooks in diagnosis and treatment.^{8,12}

Mucoepidermoid Carcinoma Translocated-1–Mastermind-Like Gene 2 Translocation

The most common genetic alteration in MECs is a unique translocation t(11;19)(q21;p13) producing a fusion transcript of exon 1 of the mucoepidermoid carcinoma translocated-1 gene (*MECT1* [aka *CRTC1*]) at 19p13 with exons 2 through 5 of a mastermind-like gene (*MAML2*) at 11q21.¹³ The fusion transcript can activate transcription of targets in the Notch pathway and can be present in 38% to 81% of MECs of the salivary gland.¹⁴⁻¹⁸ Specifically, it has been demonstrated that dysregulated Notch signaling underlies the pathogenesis of other malignancies, and the *MECT1-MAML2* transcript can activate the Notch target gene *Hes-1* (hes family basic helix-loop-helix transcription factor 1) in the absence of Notch ligand.¹⁹ The *MECT1-MAML2* transcript can also be recruited to 3',5'-cyclic adenosine monophosphate (cAMP)-responsive element-binding protein (CREB) sites to activate CREB-inducible genes that regulate cell proliferation and differentiation.^{13,19} This biologic effect of deregulated cAMP signaling may be essential for tumor cell growth.²⁰

Presence of the fusion transcript can be identified in low-grade and high-grade MECs but is associated with a significantly better prognosis (less distant metastasis, higher disease-specific and overall survival, reduced local recurrence).^{15,18,21,22} This translocation is so specific for MEC that further studies have suggested that translocation-negative, high-grade MEC may be more appropriately categorized as a different tumor type altogether.^{15,21} In fact, multiple studies have suggested that most *MECT1-MAML2* fusion-positive MECs are of the low-grade and intermediate-grade types and that high-grade MECs are a distinctive group of tumors.²³

Other Genetic Considerations in MEC

In MECs, the overexpression of epidermal growth factor receptor (*EGFR*) and human epidermal growth factor receptor 2 (*HER2*) has been explored. *EGFR* and *HER2*

overexpression was present in a minority of MECs and was associated with higher rate of metastasis and worse overall survival.^{24,25} Other evidence indicates that *HER2* and *EGFR* copy number variations can be observed in high-grade MEC, irrespective of *MECT1-MAML2* fusion status, offering another “hit” in the progression to malignancy and dedifferentiation.²³ Overall, fusion-positive tumors have lower copy number variations compared with fusion-negative tumors, with the most frequent copy number variations detected in a variety of TSGs, such as deleted in colorectal carcinoma (*DCC*), SMAD family member 4 (*SMAD4*), cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/B*), and oncogenes, such as LYN proto-oncogene SRC family tyrosine kinase (*LYN*), v-mos Moloney murine sarcoma viral oncogene homolog (*MOS*), and pleomorphic adenoma 1 (*PLAG1*).²⁶

Another specific genetic alteration that has been investigated in conjunction with the *MECT1-MAML2* fusion is deletion in the *CDKN2A/p16* gene. Fusion-positive MEC cases with *CDKN2A* deletion or hyper-methylation are associated with metastases and death, and patients who have MEC with better survival do not have this deletion.²⁷ Fusion-negative cases with poor survival also have a *CDKN2A* deletion of methylation, suggesting that the p16 pathway may be responsible for additional events in the pathogenesis of MEC.

Taken together, Jee et al proposed that MECs should be thought of as 3 distinct groups of tumors: 1) a low-grade, fusion-positive MEC with few genomic imbalances and a good prognosis (fewer recurrences, metastases, and disease-related deaths); 2) a high-grade, fusion-positive MEC with other genomic imbalances and an unfavorable prognosis; and 3) a high-grade, fusion-negative adenocarcinoma (based on molecular characterization) with multiple genomic imbalances and an unfavorable prognosis.²⁶

Other less frequently detected MEC-related fusions involve other members of the *MECT/CRTC* family. A *CRTC3-MAML2* fusion has been discovered in 6% of MECs and appears to be mutually exclusive with the *CRTC1-MAML2* fusion transcript. However, it is not associated with significant differences in disease-free survival compared with the *CRTC1-MAML2* fusion.²⁸

The potential role of high-risk human papilloma virus (HPV) in MEC remains controversial. Because high-risk HPV has been identified as a major prognostic bio-marker for oropharyngeal squamous cell carcinoma (SCC), there is great interest in exploring the role that HPV may play in other types of head and neck cancer. An initial study reported that E6/7 oncogene transcripts of HPV type 16 (HPV16) and HPV18 were identified in 30% and 13% of MECs, respectively, using reverse transcriptase-polymerase chain reaction.²⁹ However, in subsequent studies, no detectable high-risk HPV was detected by in situ hybridization in MECs, and there was no significant correlation between HPV status and *MECT1-MAML2* status.^{30,31}

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (ACC) is a rare salivary gland malignancy with a yearly incidence of from 3 to 4.5 cases per million, but it is the most common malignant tumor to arise from

the minor salivary glands.^{32,33} Clinically, ACC has a rather unusual and indolent course characterized by slow growth but late distant recurrence. Although most patients with ACC are alive at 5 years, a majority of patients die from their disease. Even from 5 to 20 years after diagnosis, the number of deaths is equal between ACC and other competing causes.^{34,35}

Histologically, ACC is characterized by a mixture of myoepithelial and luminal cells that grow in a cribriform, tubular, or solid pattern. Solid tumors are considered the highest grade of ACC and are associated with a worse prognosis, specifically advanced stage and development of distant metastasis. Tumor cells are small, cuboidal, and deeply basophilic with little cytoplasm.³⁶ Perineural invasion is also an unfavorable prognostic factor and is associated with distant metastasis.³³ The mechanisms of ACC for both tumorigenesis and invasion are poorly understood, and current research in ACC has a strong focus on the potential genetic alterations that lead to these processes.

Myeloblastosis and the Myeloblastosis-Nuclear Factor I/B Fusion

Similar to MECs, translocations have been studied in ACCs for the purpose of both molecular diagnostic tools and target-specific therapies. An important discovery was made when Persson et al observed that a recurrent t(6;9)(q22-23;p23-24) translocation in ACC tumors consistently resulted in a fusion of the myeloblastosis (*MYB*) oncogene to the transcription factor nuclear factor I/B (*NFIB*).³⁷ The *MYB-NFIB* fusion oncogene can be identified in approximately 1/3 to 1/2 of salivary ACCs and is not observed in other salivary gland tumors.^{38,39} *MYB* has an important role in cell proliferation, apoptosis, and differentiation; and downstream targets of *MYB* include mast/stem cell growth factor receptor (proto-oncogene c-Kit or tyrosine protein kinase Kit [c-kit]), cytochrome c oxidase subunit II (*cox-2*), and B-cell chronic lymphocytic lymphoma/leukemia 2 (*bcl2*).⁴⁰

Studies have demonstrated that *MYB* is overexpressed in the majority of ACCs that have *MYB-NFIB* fusions, but is also overexpressed in fusion-negative ACCs, suggesting that *MYB* may be crucial in the pathogenesis of ACC.³⁸ It is suspected that the mechanism for *MYB* up-regulation is caused by loss of its the 3'-untranslated region, which includes regulatory micro-RNA target sites. Thus, translocation of other sequences to the flanking sites of the *MYB* gene can also lead to *MYB* overexpression.⁴¹ The methylation status of the *MYB* promoter has also been investigated. Cytosine-guanine (CpG) islands in the *MYB* promoter did not exhibit differential methylation between ACC and normal salivary gland samples, suggesting that promoter hypomethylation does not contribute to the differential expression of *MYB* in ACC.⁴²

The clinical significance of *MYB* overexpression in ACC remains a mystery. One study indicated that high *MYB* expression was associated with worse overall patient survival.⁴¹ However, more recent studies determined that *MYB-NFIB* tumor status and individual *MYB* expression were not significantly associated with disease-free or overall survival.^{40,43} More investigations are needed to better understand the exact role that *MYB* plays in the development and progression of ACC. Currently, there are no drugs available to target either the *MYB-NFIB* fusion gene or the *MYB* pathway.⁴⁴

Cell Surface Receptors and Ligands Gain-of-function mutations in cell surface growth factors are a common feature of many malignancies and thus have been explored extensively in ACC. In general, luminal cells in ACC express high amounts of *c-kit* (aka cluster of differentiation 117 [CD117], a tyrosine kinase receptor), and myoepithelial cells express large amounts of *EGFR*.^{45,46}

The *c-kit* transmembrane tyrosine kinase receptor is structurally related to platelet-derived growth factor and colony-stimulating factor-1 receptors. Expression of *c-kit* is often identified in ACCs and MECs, but common genetic alterations in *c-kit* observed in other types of cancers (ie, alterations in exons 11 and 17) are not present in salivary gland cancers.⁴⁷ Nonetheless, *c-kit* expression in ACC does correlate with tumor grade, suggesting that there may be an alternative, unknown mechanism for *c-kit* activation in ACC.⁴⁸

Investigations into this mechanism have demonstrated copy number gains of *c-kit* in a few ACCs.⁴⁹ More recently, Tang et al identified a *c-kit*-associated zinc-finger transcription factor (Slug) that may act as a mediator of epithelial-mesenchymal transitions⁵⁰ and could be associated with worse TNM stage, perineural invasion, locoregional recurrence, and distant metastases.⁵¹ Studies into *c-kit* have promising potential for targeted therapies, because the popular drug imatinib can inhibit *c-kit* receptors. Unfortunately, clinical trials involving imatinib in patients with ACC have not yielded positive results.⁵²

EGFR and *HER2* can be significantly overexpressed in all types of salivary gland malignancies, and *EGFR/HER2* gene status correlates with tumor stage, tumor grade, disease-specific survival, and loss of phosphatase and tensin homolog (*PTEN*).^{24,53} In ACCs specifically, it has been observed that *EGFR* is overexpressed, whereas *HER2* expression status remains controversial.^{54,55} Over-expression of epiregulin, an *EGFR* ligand, can promote in vitro migration and invasion in an ACC cell line. These effects may be mediated through activation of extracellular signal-regulated kinases 1 and 2 (*ERK1/2*), protein kinase C (*Akt*), and *Cox-2*.⁵⁶ *EGFR* expression levels are correlated with worse histologic grade but not disease-free or overall survival.⁵⁷ *EGFR*-targeted therapies like erlotinib have not yet been studied in depth among patients with ACC. The exact role of *EGFR* in ACC pathogenesis remains in question.

Important Epigenetic Changes in ACC Epigenetic alterations like DNA methylation and histone acetylation are important factors in human carcinogenesis. Methylation of cytosines in CpG islands in gene promoters can lead to transcriptional inactivation by blocking RNA polymerase binding sites and thus inactivate TSGs. Similarly, hypomethylation of these sites may lead to relative overexpression of oncogenes. The advent of quantitative methylation-specific polymerase chain reaction has allowed for researchers to take a closer look at the epigenetic differences between cancer and normal salivary glands.

Quantitative methylation-specific polymerase chain reaction has demonstrated that salivary gland cancers have increased methylation in several TSGs, including adenomatous polyposis coli (*APC*); amyloid β precursor protein-binding family A, member 1 (*Mint 1*); P-glycoprotein 9.5 (*PGP9.5*); retinoic acid receptor β (*RAR- β*); and TIMP metalloproteinase inhibitor 3 (*Timp3*).⁵⁸ Similar methods have also demonstrated that several cyclin-dependent kinase inhibitors (CKIs) are frequently methylated in ACCs.⁵⁹ CKIs are cell cycle regulators

and tumor suppressors in various cancers. Hypermethylation of 1 specific CKI, *p27*, may lead to its down-regulation and contribute to disruption of the cell cycle in ACC tumorigenesis.⁵⁹ Large-scale microarrays comparing ACC with normal salivary tissues have reported hypermethylation at up to 32 CpG islands; these islands were associated with genes involved in developmental, apoptotic, and other fundamental cellular pathways. One in particular, the engrailed homeobox 1 (*EN1*) gene, was correlated with histologic tumor grade and patient survival and has some potential as a possible biomarker.⁶⁰

A genome-wide screen for epigenetic oncogene candidates also identified aquaporin-1 (AQP1) and suprabasin (*SBSN*) as promising candidates.⁶¹ Aquaporin is a small transmembrane protein responsible for water transport across membranes. The AQP1 promoter is significantly hypomethylated in ACC tumors compared with normal salivary gland tissues; this promoter hypomethylation is associated with increased AQP1 expression. In addition, AQP1 promoter hypermethylation is associated with improved overall survival.⁶² *SBSN* plays an important role in epidermal differentiation and maintaining anchorage-independent and anchorage-dependent cell proliferation in ACC. *SBSN* is significantly hypomethylated and up-regulated in ACC tumors compared with normal salivary glands, and this hypomethylation is associated with an increased risk of regional recurrence.⁶³

Other Genetic Considerations in ACC

The potential role of epigenetics alterations in ACC is not at all surprising, considering the finding that 2 separate, large, whole-exome sequencing studies of ACC tumors have revealed a large number of variants in chromatin remodeling genes.^{64,65} These genes, which are responsible for histone modification and epigenetic regulation, are also often mutated in breast ACC.⁶⁶ Stephens et al reported aberrations in chromatin remodeling genes in half of all salivary ACC samples sequenced, including some chromatin regulator genes that had not previously been implicated in cancer (SW/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 2 [*SMARCA2*]; chromodomain helicase DNA-binding protein 2 [*CHD2*]; bromodomain containing 2 [*BRD2*]; AT-rich interaction domain containing 5B [*ARID5B*]; and lysine-specific demethylase 5A [*KDM5A*]).⁶⁴ Another study similarly reported chromatin regulator mutations in 35% of ACC tumors tested.⁶⁵

Using whole-exome sequencing, Ho et al also identified recurrent mutations in the fibroblast growth factor–insulin-like growth factor–phosphatidylinositol 3-kinase (FGF-IGF-PI3K) pathway in 30% of tumors, establishing a potential targetable pathway for future therapy. However, relatively few consistent, individual mutations were identified in either study, confirming that ACC maintains a stable genome aside from the frequently identified translocation.

In addition to *MYB-NFIB* translocations, other cytogenetic changes have also been explored in ACC. Because ACCs do not display the degree of genomic instability associated with many other cancer types,⁶⁷ many believe that chromosome regions displaying loss of heterozygosity are not simply nonspecific changes but, rather, are important clues to the pathogenesis of ACC. ACC tumors have exhibited copy number losses at chromosome 12q12-q13 and 1p32-36 and gains at 22q12-q13, 8, 16p, 17q, and 18.⁶⁰ Rutherford et al

interpret the high incidence of chromosome 12 deletions as consistent with the presence of specific TSGs on this chromosome.⁶⁸ Genomic deletions in chromosome 6 can also occur in up to 57% of ACCs, and the hotspot of deletion (6q24.1-q25.1) contains candidate TSGs, including pleomorphic adenoma of the salivary gland gene like 1 (*PLAG1*) and large tumor suppressor 1 (*LATS1*).⁶⁸

The scarcity of knowledge about the pathogenesis of ACC has also prompted investigators to explore novel methods in the detection of genetic abnormalities. Whole mitochondrial sequencing has demonstrated that ACC tumors contain a high incidence of mitochondrial mutations.⁶⁹ The clinical and molecular implications of these mutations are not yet known. A comprehensive summary of the genetic alterations involved in ACC as well as all the other tumor types featured in this review is provided in Table 1.⁷²

Salivary Duct Carcinoma

Salivary duct carcinoma (SDC) can account for 5% to 10% of salivary carcinomas, often occurs in men aged >50 years, and is one of the most aggressive cancers that can arise in the salivary glands.^{70,71} It is classified as an aggressive adenocarcinoma that histologically resembles high-grade breast ductal carcinoma and can arise as a malignant component of carcinoma ex pleomorphic adenoma.⁷⁰ On immunohistochemistry, cells are usually positive for cytokeratin 7 (CK7), CK20, and HER2 but negative for S100. Unlike ductal carcinoma of the breast, the majority of SDCs do not stain positive for the estrogen receptor.⁷⁰ Instead, from 67% to 83% of SDCs express the androgen receptor (AR).⁷⁰ Clinically, SDC has an aggressive course, and patients commonly develop regional and distant metastases. Most die from the disease within 3 to 4 years of diagnosis.⁷¹

Investigations into the pathogenesis of SDC have revealed overexpression of *HER2* in greater than 1/3 of patients with SDC, similar to its breast counterpart.⁷¹ Overexpression of *p53* and high frequency of DNA aneuploidy are also common.⁷³ Both *HER2* and *p53* overexpression in SDCs are correlated with early local disease recurrence, distant disease metastasis, and survival rates.^{6,74} Conversely, expression of AR is associated with greater disease-free survival.⁷⁵ Other mutations described in SDC include v-Raf murine sarcoma viral oncogene homolog B (*BRAF*); phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (*PIK3CA*); receptor tyrosineprotein kinase erbB-2 (*ERBB2*); *PTEN*; and *EGFR*.⁷⁶⁻⁸⁰

On the basis of the differential expression and prognostic value of HER2 and AR in SDCs, some investigators have proposed that SDC should be classified based on the presence or absence of AR and HER2.⁷⁰ This not only would allow for prognostic stratification but also would make way for new therapeutic strategies directly targeted toward these molecules. The HER2 inhibitor trastuzumab has exhibited great success in the treatment of breast cancer. In patients with progressive SDC, trastuzumab may improve disease-free and overall survival.⁷¹ Androgen-deprivation therapies (ADTs) have also been explored in small studies and have produced promising results.⁷⁰ One case series of 10 patients with recurrent or metastatic SDC who received ADT had a median progression-free survival of 12 months.⁸¹

Other reports suggest extending ADT beyond patients with advanced disease, using a combination of ADT and radiation as definitive therapy in poor surgical candidates.⁸²

Mammaryanalogue Secretory Carcinoma

Mammary analogue secretory carcinoma (MASC) is a relatively new salivary gland tumor first recognized in 2010 that histologically resembles secretory carcinoma of the breast.⁸³ It is an infiltrative tumor that grows in microcystic and tubular patterns, with PAS-positive/diastase-resistant secretory material within the luminal spaces,⁸⁴ and can often be misclassified as acinic cell carcinoma.⁸⁵ Since its definition, many tumors that were previously labeled as acinic cell carcinomas have now been reclassified as MASCs.⁷⁰ On immunohistochemistry, MASC can be distinguished from other salivary gland tumors by its strong positivity for S100, mammaglobin, cytokeratin, and vimentin.⁸⁶ Clinically, MASC can occur at any age and has a slight male predominance.⁷⁰ Although few long-term follow-up studies have been conducted, it is considered a low-grade neoplasm with recurrence and metastases rates <20%. However, MASC usually has a more aggressive clinical course compared with its breast counterpart, and it has the capacity for high-grade transformation.⁸⁶

The genetic hallmark of this tumor, similar to its counterpart in the breast, is a translocation between the ets variant 6 (*ETV6*) and neurotrophic tyrosine kinase, receptor, type 3 (*NTRK3*) genes. This t(12;15)(p13;q25) translocation produces a fusion product that contains the transcriptional regulator *ETV6* fused with the membrane receptor kinase *NTRK3*, which activates cell proliferation and survival.⁸³ Although the exact function of this fusion product is not yet known, it may be related to the high expression of signal transducer and activator of transcription molecule 5a (*STAT5a*) in MASCs.⁸³ The fusion product, a chimeric tyrosine kinase, has the ability to activate both the rat sarcoma (Ras) mitogen-activated protein (MAP) kinase (Ras-MAP) pathway and the PI3K-Akt pathway.⁷¹ One case series of 14 Japanese patients with MASC patients indicated that, although all had an *ETV6* split, only 43% had the fusion transcript, suggesting that *EVT6* may also occasionally fuse with non-*NTRK3* genes.⁸⁷

The significance of this *ETV6-NTRK3* fusion for future treatment is not well understood either. The transcript target has promising pharmaceutical potential, because some *ETV6-NTRK3*-positive leukemias have responded well to tyrosine inhibitors.⁸⁸ More research is needed to characterize the exact role that this fusion product plays in prognosis and management.

Hyalinizing Clear Cell Carcinoma

Hyalinizing clear cell carcinoma (HCCC) is an epithelial malignancy of the salivary glands composed of clear cells that form nests and cords. Because many other salivary gland tumors can have a clear cell component, clear cell carcinoma is a diagnosis of exclusion.⁸⁶ Histologically, the clear cells grow in a pattern of hyalinization with focal mucinous differentiation. HCCC is a very rare, low-grade tumor with a very good prognosis and rare metastases.⁷¹

Recently, a disease-defining translocation in the Ewing sarcoma RNA-binding protein 1 (*EWSR1*) gene was identified in >80% of HCCCs and may be used to distinguish it from its many mimics.⁷⁰ The most common fusion, a t(12;22)(q13;q12) translocation, produces a fusion transcript consisting of the genes *EWSR1* and activating transcription factor 1 (*ATF1*).⁷² Although the translocation appears to be very specific to HCCC, its exact function is not well known. It is noteworthy that this specific translocation is also present in a majority of odonogenic clear cell carcinomas, suggesting a biologic link between the 2 malignancies.⁸⁶

Carcinoma Ex Pleomorphic Adenoma

Carcinoma ex pleomorphic adenoma is a carcinoma that arises from a benign pleomorphic adenoma and can account for 10% to 15% of salivary gland cancers.⁸ The carcinomatous component of this tumor is usually an aggressive, high-grade adenocarcinoma, but it also can comprise other types of carcinomas.⁸ Because of the tremendous diversity in its histologic appearance, recent molecular studies have attempted to identify the unifying genetic changes that define this tumor. After all, pleomorphic adenoma, the benign counterpart to carcinoma ex pleomorphic adenoma, is characterized by a very specific pattern of translocations involving the transcription factors *PLAG1* and high-mobility group AT-hook 2 (*HMGA2*) and various fusion partner genes.⁸⁹ Small studies have demonstrated that carcinoma ex pleomorphic adenomas also harbor common rearrangements and copy number variations in the pleomorphic adenoma-specific genes *PLAG1* and *HMGA2*.⁷² The consequences of these rearrangements are not well understood.

Salivary Gland SCC

Although SCC is the most common form of head and neck cancer, primary SCC is rare in the salivary glands, and only 7% of parotid cancers are identified as primary SCC.⁹⁰ Recent work in mouse models has demonstrated that mice with increased Wnt/ β -catenin signaling rapidly develop salivary gland SCC.⁹¹ When cancer stem cells were isolated from these SCC tumors, investigators were able to demonstrate that the β -catenin pathway drove tumor proliferation through histone modifications at the promoters of stem cell-associated genes.⁹¹ It is noteworthy that mutations in components of the Wnt/ β -catenin pathway have also recently been implicated in ACC—another type of salivary gland malignancy that displays a high prevalence of epigenetic aberrations.⁶⁰

Acinic Cell Carcinoma

Acinic cell carcinoma is traditionally considered another low-grade tumor with a good prognosis; however, like many other salivary gland cancers, late recurrence and metastatic disease can occur.⁸ Very little is known about the genetic alterations that contribute to this disease. Since the emergence of MASCs as a distinct tumor category, the defining characteristics of acinic cell carcinoma have come under question. New evidence suggests that it may be a far more aggressive tumor than originally reported.⁹² The mammalian target of rapamycin (mTOR) pathway has been explored in the pathogenesis of acinic cell carcinoma, and some immunohistochemical evidence supports the overactivation of this

pathway.⁷¹ Further evidence implicating the mTOR pathway in acinic cell carcinoma may lead to new drug trials involving the many mTOR pathway inhibitors (ie, rapamycin).

Conclusion

Salivary gland cancers are a histologically and molecularly heterogeneous group of tumors that have distinct genetic origins. Currently, the mainstay of treatment for salivary gland cancer is surgical resection and postoperative radiotherapy. At this point, chemotherapy and targeted therapy play only a limited role. In fact, the most recent National Comprehensive Cancer Network guidelines only recommend systemic therapy for unresectable, persistent, or recurrent disease. Platinum-based agents have been the most well studied systemic therapies, but the evidence behind this practice is solely based on a mild response observed in nonrandomized studies.⁹³

Recent discoveries in the genetic alterations of each tumor type have helped us better define and categorize these salivary malignancies. However, although many candidate oncogenes and TSGs have been discovered, the diagnostic and therapeutic potential of these genetic anomalies remains to be seen. Although the genetic makeup of each tumor type appears to be unique, there are common pathways and themes shared among the various types of salivary gland tumors—abnormalities in epigenetic regulation, oncogenic fusion products, and overexpression of cell surface receptors. Therefore, effective drug development should focus on targeting the key players upon which multiple oncogenic pathways converge. Some targeted therapy clinical trials have begun to make progress, but several promising aforementioned leads require more evidence to impact clinical practice. Future systemic therapy for salivary gland cancers hopefully will use a combination of whole-exome tumor sequencing and specific molecular inhibitors to form individualized treatment regimens for every patient afflicted with this disease.

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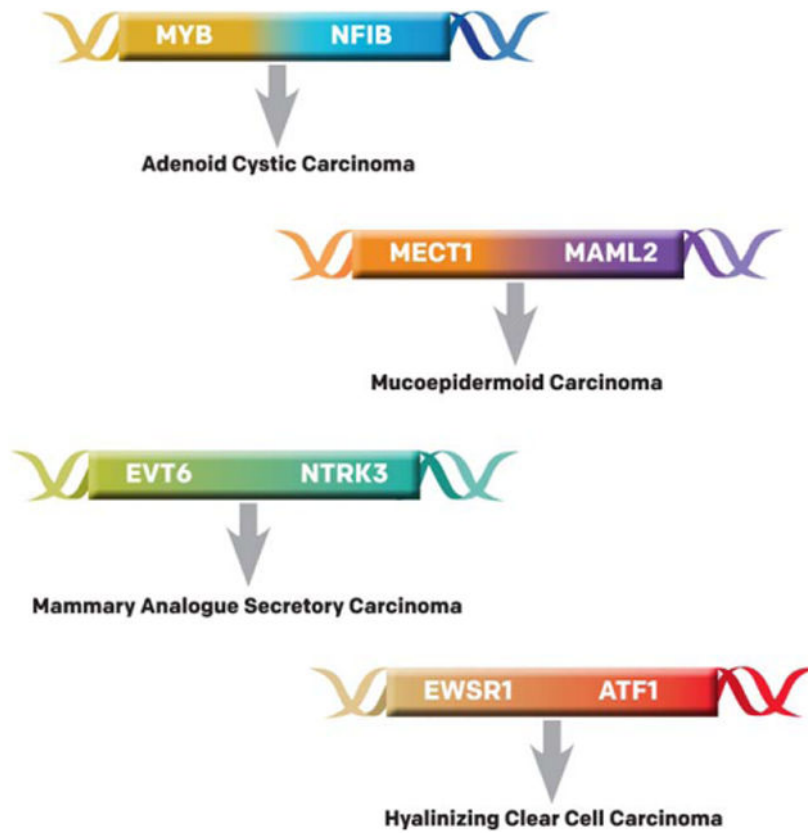


Figure 1. Known translocations identified in salivary gland cancers are illustrated. *ATF1* indicates activating transcription factor 1; *EVT6*, ets variant 6; *EWSR1*, Ewing sarcoma binding protein 1; *MAML2*, mastermind-like transcriptional coactivator 2; *MECT1*, mucoepidermoid carcinoma translocated-1; *MYB*, v-myb avian myeloblastosis viral oncogene homolog; *NFIB*, nuclear factor I/B; *NTRK3*, neurotrophic tyrosine kinase, receptor, type 3.

Table 1
Important Genetic Alterations in Salivary Gland Cancers

Cancer Type/Genetic Alteration	Gene(s)	Role in Tumor Pathogenesis
Mucoepidermoid carcinoma (MEC) Translocation, fusion transcript	<i>MECT1-MAML2</i> (O'Neill 2009 ¹³)	Activate the Notch target gene <i>Hes-1</i> in the absence of Notch ligand (Kaye 2006 ¹⁹); activate CREB inducible genes that regulate cell proliferation and differentiation (O'Neill 2009, ¹³ Kaye 2006 ¹⁹) Exact function unknown
Copy number variation	<i>CRTC3-MAML2</i> (Nakayama 2009 ²⁸) <i>HER2, EGFR</i> (Ettl 2012 ²⁴)	Growth factor receptors, overexpression associated with poor rates of metastases and survival (Ettl 2012 ²⁴)
Epigenetic	<i>DCC, SMAD4</i> (Jee 2013 ²⁶) <i>LYN, MOS, PLAG⁶</i> (Jee 2013 ²⁶) <i>CDKN2A/p16</i> (Anzick 2010 ²⁷)	Various tumor suppressor genes, exact role in MEC unknown (Jee 2013 ²⁶) Various oncogenes, exact role in MEC unknown (Jee 2013 ²⁶) Tumor suppressor gene, cell cycle regulator, deletion/hypermethylation associated with poor survival (Anzick 2010 ²⁷)
Adenoid cystic carcinoma (ACC) Translocation, fusion transcript	<i>MYB-NFIB</i> (Persson 2009 ³⁷)	MYB is an oncogene involved in cell proliferation, apoptosis, and differentiation; downstream targets include c-kit, cox-2, and bcl2 (Bell 2011 ⁴⁰); controversial association with patient survival (Mitani 2011, ⁴¹ Rettig 2015 ⁴³)
Epigenetic changes	<i>APC, Mint1, PGP9, RAR-β, Timp3</i> (Durr 2010 ⁵⁸) <i>p27</i> (Daa 2008 ⁵⁹)	Various tumor suppressor genes, hypermethylated in ACC, exact role unknown (Durr 2010 ⁵⁸) Cell cycle regulator hypermethylated in ACC, leads to down-regulation and disruption of cell cycle (Daa 2008 ⁵⁹), role in prognosis unknown
	<i>EN1</i> (Liu 2012 ⁶⁰)	Homeobox gene hypermethylated in ACC, correlates with histologic tumor grade and patient survival (Liu 2012 ⁶⁰)
	<i>AQ1</i> (Shao 2011, ⁶¹ Tan 2014 ⁶²)	Transmembrane protein for water transport, hypomethylated in ACC, hypermethylation is associated with better survival (Shao 2011, ⁶¹ Tan 2014 ⁶²)
	<i>SBSN</i> (Shao 2012 ⁶³)	Involved in epidermal differentiation, anchorage-independent growth, hypomethylated in ACC and associated with increased risk of recurrence (Shao 2012 ⁶³)
Copy number losses/deletion	12q12-q13, 1p32-36, and gains at 22q12-q13, 8, 16p, 17q, 18 (Liu 2012 ⁶⁰)	High presence of tumor suppressor genes at these loci, exact role in ACC unknown (Liu 2012 ⁶⁰)
	Hotspot 6q24.1-q25.1 including <i>PLAG1, LATS1</i> (Rutherford 2006 ⁶⁸)	Tumor suppressor genes, exact role in ACC unknown (Rutherford 2006 ⁶⁸)
Copy number gains/up-regulation	c-kit (Holst 1999, ⁴⁸ Freier 2005 ⁴⁹)	Transmembrane tyrosine kinase receptor, overexpression associated with worse tumor grade (Holst 1999, ⁴⁸ Freier 2005 ⁴⁹)
	<i>EGFR</i> (Monteiro 2009 ⁵⁷)	Growth factor receptor, overexpression associated with worse histologic grade (Monteiro 2009 ⁵⁷)
Salivary duct carcinoma (SDC) Aneuploidy/up-regulation	<i>HER2</i> (Zhu 2015 ⁶)	Growth factor receptor, overexpression in SDC associated with worse recurrence rates, metastases, and survival (Zhu 2015 ⁶)
	<i>p53</i> (Zhu 2015 ⁶)	Plays a role in genome stability, overexpression in SDC associated with worse recurrence rates, metastases, and survival (Zhu 2015 ⁶)
	AR (Simpson 2014 ⁷⁰)	Androgen receptor (AR)-negative tumors are more aggressive than AR-positive tumors (Simpson 2014 ⁷⁰)
Mammary analogue secretory carcinoma (MASC) Translocation	<i>ETV6-NTRK3</i> (Stenman 2014 ⁷¹)	Fusion product is a chimeric tyrosine kinase with the ability to activate the Ras-MAP pathway and PI3K-

Cancer Type/Genetic Alteration	Gene(s)	Role in Tumor Pathogenesis
		Akt pathway (Stenman 2014 ⁷¹), role in prognosis unknown
Hyalinizing clear cell carcinoma (HCCC) Translocation	<i>EWSR1-ATF</i> (Stenman 2013 ⁷²)	Exact function unknown (Stenman 2013 ⁷²)
Carcinoma ex pleomorphic adenoma Rearrangements	<i>PLAG1, HMGA2</i>	Transcription factors that can undergo a variety of rearrangements; consequences of rearrangements unknown (Stenman 2013 ⁷²)

Abbreviations: Akt, protein kinase B; *APC*, adenomatosis polyposis coli; *AQP1*, aquaporin 1; *ATF*, activating transcription factor; bcl2, B-cell chronic lymphocytic lymphoma/leukemia 2; *CDKN2A/p16*, cyclin-dependent kinase inhibitor 2A; c-kit, mast/stem cell growth factor receptor (proto-oncogene c-Kit or tyrosine protein kinase Kit); cox-2, cytochrome c oxidase subunit II; CREB, cyclic AMP responsive binding protein; *CRTC3*, *CREB* regulated transcription coactivator 3; *DCC*, deleted in colorectal carcinoma; *EGFR*, epidermal growth factor receptor; *EN1*, engrailed homeobox 1; *ETV6*, ets variant 6; *EWSR1*, Ewing sarcoma RNA binding protein 1; *HER2*, human epidermal growth factor receptor 2; *Hes-1*, hes family basic helix-loop-helix transcription factor 1; *HMGA2*, high-mobility group AT-hook 2; *LATS1*, large tumor suppressor kinase 1; *LYN*, LYN proto-oncogene, Src family tyrosine kinase; MAP, mitogen-activated protein; *MAML2*, mastermind-like transcriptional coactivator 2; *MECT1*, mucoepidermoid carcinoma translocated-1; Mint1, amyloid β precursor protein-binding family A, member 1 (*APBA1*) adaptor protein; MOS, v-mos Moloney murine sarcoma viral oncogene homolog; *MYB*, v-myb avian myeloblastosis viral oncogene homolog; *NFIB*, nuclear factor I/B; *NTRK3*, neurotrophic tyrosine kinase, receptor, type 3; *p16*, *CDKN2A* multiple tumor suppressor; *p27*, cyclin-dependent kinase inhibitor 1B; *p53*, tumor protein 53; *PGP9*, P-glycoprotein 9; PI3K, phosphoinositide 3-kinase; *PLAG1*, pleomorphic adenoma 1; *PLAG4*, pleomorphic adenoma 4; *RAR- β* , retinoic acid receptor β ; Ras, rat sarcoma; *SBSN*, suprabasin; *SMAD4*, SMAD family member 4; *Timp3*, TIMP metalloproteinase inhibitor 3.

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