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The landscape of gene fusions and somatic mutations in salivary gland neoplasms – Implications for diagnosis and therapy

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SUMMARY

Recent studies of the genomic landscape of salivary gland tumors have provided important insights into the molecular pathogenesis of these tumors. The most consistent alterations identified include a translocation-generated gene fusion network involving transcription factors, transcriptional coactivators, tyrosine kinase receptors, and other kinases. In addition, next-generation sequencing studies of a few subtypes of salivary neoplasms have revealed hotspot mutations in individual genes and mutations clustering to specific pathways frequently altered in cancer. Although limited, these studies have opened up new avenues for improved classification and targeted therapies of salivary gland cancers. In this review, we summarize the latest developments in this field, focusing on tumor types for which clinically important molecular data are available.

Introduction

Salivary gland tumors are a heterogeneous group of benign and malignant neoplasms that pose significant diagnostic difficulties due to the multitude of histopathologic subtypes and the rarity of many of the lesions [1]. There is also morphologic overlap between several subtypes, making it difficult to determine whether they are, in fact, separate entities or variants of the same spectrum [1]. Clinically, malignant salivary neoplasms may vary widely in prognosis, patterns of spread, recurrence, and metastasis. Most low-grade malignancies are successfully treated by radical surgery. However, there are few or no treatment options for unresectable tumors, which are often resistant to chemotherapy and radiation therapy [2,3]. Few if any targeted therapies are effective for salivary gland cancers [3]. Thus, new treatment strategies are needed.

Recent molecular studies have uncovered a chromosome translocation-generated gene fusion network in salivary neoplasms (Fig. 1), opening new avenues for molecular classification and improved diagnosis [4,5]. Importantly, gene fusions are also targets for new therapies, as demonstrated by the successful use of the tyrosine kinase inhibitor imatinib to treat patients with *BCR-ABL* fusion-positive chronic myeloid leukemia [6]. This review will focus on tumor types for which we have significant knowledge about gene fusions and other molecular alterations and discuss the most recent developments, highlighting new therapeutic strategies.

Pleomorphic Adenoma (PA) and Carcinoma-ex-Pleomorphic Adenoma (Ca-ex-PA)

PA is the most common histologic subtype of salivary neoplasm in both adults and children [1]. It is a benign, encapsulated, and rather slow growing tumor that can occur both in the major and minor glands. PAs may occasionally be difficult to manage clinically, as they tend to recur and may undergo malignant transformation. Cytogenetic analysis of more than 400 PAs has shown that they are characterized by in particular translocations involving chromosome bands 8q12 (>50% of the cases) and 12q14-15 (≈15% of the cases) [4,7 unpublished data]. There are also subgroups of PA with nonrecurrent clonal rearrangements or an apparently normal karyotype [4,7]. The targets of the 8q12 and 12q14-15 translocations are the transcription factors PLAG1 and HMGA2 [8,9]. The rearrangements lead to gene fusions with promoter swapping between *PLAG1* and different fusion partners and between the 5′-part of *HMGA2* (including the DNA-binding domains) and the 3′-part of various fusion partners (Fig. 1 and Table 1) [4,7]. The latter fusions are structurally similar to the *MYB* fusions in adenoid cystic carcinoma (ACC) (see below; Fig. 2A) [10]. Thus, these fusions disrupt the 3′-ends of both genes, leading to loss of negative regulatory elements and overexpression of *HMGA2* and *MYB* due to fusion or juxtaposition of enhancer elements contributed by the translocation partner genes, including

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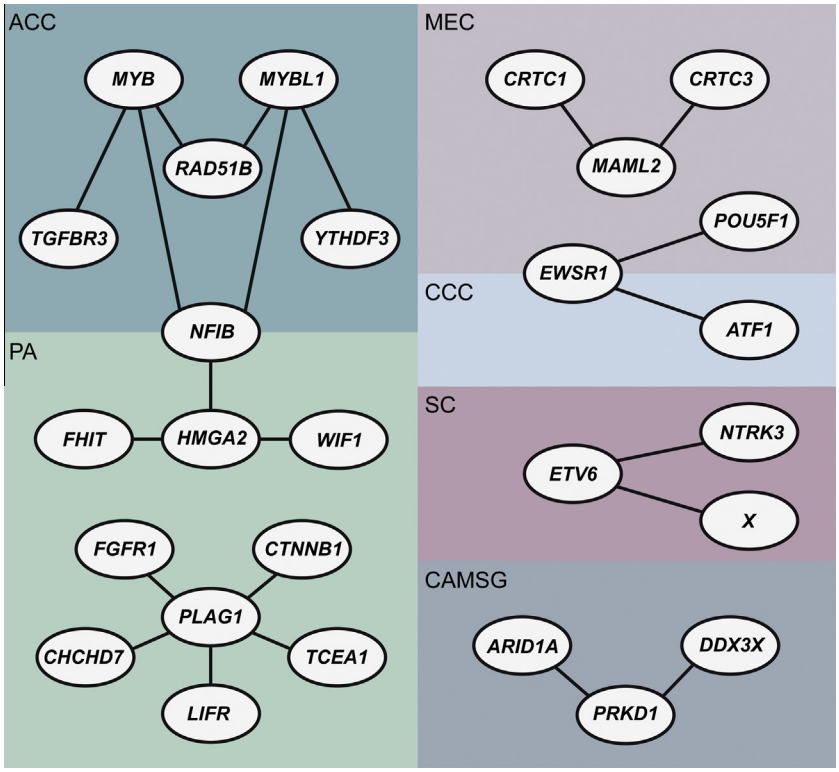

Fig. 1. A translocation-generated gene fusion network in salivary gland neoplasms involving transcription factors, transcriptional coactivators, tyrosine kinase receptors, and other kinases. ACC, adenoid cystic carcinoma; PA, pleomorphic adenoma; MEC, mucoepidermoid carcinoma; CCC, clear cell carcinoma; SC, secretory carcinoma; CAMSG, cribriform adenocarcinoma of minor salivary glands.

NFIB [9–11]. Notably, *PLAG1*-driven tumors show increased IGF and WNT signaling, suggesting that these pathways are potential targets for therapy with for example linsitinib or XAV939 (Table 1) [12–14].

Ca-ex-PA is a carcinoma that develops from a primary or recurrent PA predominantly in the parotid gland [1]. Intracapsular or minimally invasive Ca-ex-PA usually has a low rate of recurrence and regional metastasis, whereas frankly invasive tumors are more likely to be high-grade, aggressive malignancies with frequent local and distant metastases. The malignant component is most frequently a high-grade carcinoma such as salivary duct carcinoma (SDC) but may also be a myoepithelial carcinoma or any other histological subtype [1]. Not unexpectedly, Ca-ex-PA has the same patterns of translocations and gene fusions as PA, including *PLAG1* and *HMGA2* fusions (Fig. 1 and Table 1) [4,7]. High-grade tumors are usually genomically unstable and have multiple copy number alterations [15–18]. Ca-ex-PA may also show subtype-specific alterations such as amplification and/or overexpression of *HER2* (*ERBB2*) and *AR* in SDC-ex-PA [3,5,19,20]. Other genomic alterations associated with progression from adenoma to carcinoma are amplification of *HMGA2* and *MDM2*, mutation of *TP53*, del (5q23.2-q31.2), and gains/amplifications of *PLAG1*, *MYC*, and/or *EGFR* [5,19,21]. We suggest that patients with surgically unresectable Ca-ex-PA should be morphologically and molecularly subtyped to identify possible targeted therapies, such as anti-HER2 or anti-AR treatments (Table 1) in SDC-ex-PA with amplification/overexpression of these receptors [5]. Similarly, patients with *MDM2* amplification may be targeted with small-molecule inhibitors of MDM2 (e.g., MI-219 or nutlin-3 analogs) [22], which can reactivate TP53 in tumors with *MDM2*-amplification (Table 1).

Adenoid Cystic Carcinoma (ACC)

ACC is the second most common salivary malignancy. It is a slow-growing but ultimately fatal cancer with frequent local recurrences, distant metastases, and a tendency for perineural invasion [1,3,23]. ACC may also arise in the sinonasal tract, breast, prostate, lung, skin, and female genital tract [5]. Tumors arising in the head and neck usually have a poor long-term prognosis, and there is no effective systemic treatment available for patients with surgically unresectable disease [3,23]. The genomic hallmark of ACC is a t(6;9) translocation, one of the first carcinoma-specific translocations identified in human cancer [24,25]. The translocation commonly results in a fusion of the transcription factor genes *MYB* and *NFIB* (Figs. 1 and 2A and Table 1) [10].

MYB encodes an oncogenic transcription factor and regulator of stem cells [26], and *NFIB* encodes a transcription factor that controls cell proliferation and cell viability [27]. The MYB-NFIB fusions, which consist of the DNA-binding and transactivation domains of MYB fused to different parts of the 3′-end of NFIB, interrupt the C-terminal part of MYB, leading to loss of negative regulatory sequence elements and, consequently, overexpression of the fusion protein [10]. In addition to gene fusion, *MYB* may be activated by copy number gain or juxtaposition of enhancer elements from other genes, including *NFIB, RAD51B,* or *TGFBR3*, to the *MYB* locus (Figs. 1 and 2b–d and Table 1) [17,18,28]. The latter events result in overexpression of a normal MYB protein, whereas the fusion events usually result in expression of truncated MYB proteins. *MYB* activation occurs in the vast majority of ACCs, demonstrating that it is a key genomic event in the disease and therefore a potential diagnostic and therapeutic target [10,17,29–32]. In a subset of ACC, *MYB* may be replaced by the closely related gene, *MYBL1*,