Molecular Characterization of Salivary Gland Carcinomas

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Abbreviations

a.k.a.	Also known as
ACC	Acinic cell carcinoma
AdCC	Adenoid cystic carcinoma
AR	Androgen receptor
CAMSG	Cribriform adenocarcinoma of minor salivary glands
CREB	cAMP response element-binding protein
CXPA	Carcinoma ex pleomorphic adenoma
FGF-IGF-PI3K	Fibroblast growth factor-insulin-like growth factor-phosphatidylinositol 3-kinase pathway
FISH	Fluorescence in situ hybridization
HCCC	Hyalinizing clear-cell carcinoma
IDC	Low-grade intraductal carcinoma
MAPK	Mitogen-activated protein kinase
MASC	Mammary analogue secretory carcinoma
MEC	Mucoepidermoid carcinoma

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NOS	Not otherwise specified
PA	Pleomorphic adenoma
PAC	Polymorphous adenocarcinoma
PI3K	Phosphatidylinositol 3-kinase
RT-PCR	Reverse transcription polymerase chain reaction
SC	Secretory breast carcinoma
SDC	Salivary duct carcinoma
SGC	Salivary gland carcinomas

2.1 Introduction

The advent and widespread use of new genetic methods (e.g., next-generation sequencing or array technologies) has paved the way for promising advancements in our understanding of molecular tumor biology. This is also true for salivary gland carcinomas (SGC) which comprise a widely heterogeneous group of cancers [1]. Diagnosis is challenging, due to the diversity of histologic subtypes and the overlapping morphological patterns among many of these lesions. The phenotypic heterogeneity is reflected by the variety of aberrant genetic and molecular pathways contributing to the development and progression of each tumor. There are unique molecular alterations for some SGCs (Table 2.1), which will be the focus of this chapter, pointing out molecular markers that could become relevant in clinical practice. This chapter highlights markers that can be used for typization of tumors and sporadically reported and research-based markers that can be found elsewhere in the literature.

Table 2.1 Overview of recurrent alterations in salivary gland carcinomas

Diagnosis	Alteration	Gene fusion	Comments	References
MEC	t(11;19)(q21~22;p13)	*CRTC1-MAML2*	Usual good prognosis; occurs mainly in low- and intermediate-grade MECs	[2–4]
	t(11;15)(q21;q26)	*CRTC3-MAML2*		[5, 6]
	Loss of *CDKN2A*		Indicator for worse prognosis	[7]
	Hotspot mutation in *HRAS*		Occurs in ~20% of MECs	[8]
	t(6;15)(p21;q12)	*EWSR1-POU5F1*	Occur in high-grade MEC-like tumors	[9]
	Mutation of *TP53*		Occurs in intermediate- and high-grade MECs	[10]
	In-frame deletion in *POU6F2*		187Q > –	
AdCC	t(6;9)(q22~23;p23~24)	*MYB-NFIB*		[11–13]
	t(8;9)	*MYBL1-NFIB*		
	t(8;14)	*MYBL1-RAD51B*		

Table 2.1 (continued)

Diagnosis	Alteration	Gene fusion	Comments	References
MASC	t(12;15)(p13;q25)	*ETV6-NTRK3*	Same fusion as in SC of the breast	[14]
	t(12;?)	*ETV6-X* (unknown fusion partner)	Potential more aggressive than MASC with *ETV6-NTRK3* fusion	[15, 16]
HCCC	t(12;22)(q13;q12)	*EWSR1-ATF1*	Occur in high frequency in HCCC and CCOC, indicates a biologic link between these entities	[17, 18]
CXPA	t(8q12)	*CTNNB1-PLAG1*	Same fusions as described for PAs	[19–22]
		FGFR1-PLAG1		
		TCEA1-PLAG1		
		CHCHD7-PLAG1		
		LIFR-PLAG1		
	t(12q14–15)	*HMGA2-WIF1*		
		HMGA2-FHIT		
		HMGA2-NFIB		
	Amplification 12q13–15		Amplification of *HMGA2* and/or *MDM2*	
	Mutation of *TP53*			
	Mutation or amplification of *ERBB2* (HER2)			
SDC	Mutations of *TP53*, *HRAS*, *PIK3CA*, or *BRAF*			[21, 23]
	Loss or mutation of *PTEN*			
	Amplification of *ERBB2*			
	Gain of *EGFR*			
	Gain and/or overexpression of *AR* (androgen receptor)			
PAC	Hotspot mutation in *PRKD1*		p.Glu710Asp	[24]
CAMSG	t(1;14)	*ARID1A-PRKD1*		[25]
	t(14;X)	*DDX3X-PRKD1*		

AdCC adenoid cystic carcinoma, *CAMSG* cribriform adenocarcinoma of minor salivary glands, *CXPA* carcinoma ex pleomorphic adenoma, *HCCC* hyalinizing clear-cell carcinoma, *MASC* mammary analogue secretory carcinoma, *MEC* mucoepidermoid carcinoma, *PA* pleomorphic adenoma, *PAC* polymorphous adenocarcinoma, *SC* secretory carcinoma of the breast, *SDC* salivary duct carcinoma

2.2 Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy. MECs are composed of mucinous, intermediate (clear-cell), and squamoid tumor cells forming cystic and solid patterns [1]. Rarely they can also occur in other anatomic locations such as the skin, lung, maxillary sinus, and upper respiratory tract

[26–29]. MEC is traditionally graded in low-, intermediate-, and high-grade tumors. Low-grade MECs have an excellent prognosis after surgical excision with a 10-year survival rate of over 90%. In contrast, high-grade MECs have a poor prognosis. Despite intense treatment strategies, the 10-year survival rate is about 25% [1, 30]. Previous cytogenetic studies have identified a t(11;19)(q21~22;p13) translocation as a recurrent and tumor-type-specific rearrangement in MECs of the salivary glands [2]. Recent studies have shown that this rearrangement results in a fusion of *CRTC1* (a.k.a. *MECT1*, *TORC1*, and *WAMTP1*) exon 1 with exon 2–5 of *MAML2* [5], whereas a small subset of MEC shows a t(11;15)(q21;q26) translocation cytogenetically reflecting a *CRTC3-MAML2* fusion [31].

MAML2 belongs to a family of Mastermind-like nuclear proteins that act as transcriptional coactivators for Notch receptors. CRTC1 and CRTC3 are part of a family of highly conserved CREB coactivators [5, 32]. The *CRTC1-MAML2* fusion encodes a chimeric protein consisting of the CREB-binding domain of CRTC1 linked to the transactivation domain of MAML2. In particular, the fusion protein activates transcription of cAMP/CREB target genes [33, 34]. Previous studies have shown that sustained expression of the fusion is essential for tumor cell growth in salivary gland cancers that carrying the t(11;19) translocation [3]. Tumors with *CRTC1/CRTC3-MAML2* gene fusion tend to be low- or intermediate-grade. High-grade MEC are rarely fusion positive. Moreover, some clinical studies have demonstrated that patients with *CRTC1/CRTC3-MAML2*-positive MECs have increased survival and a better prognosis [4, 6, 35–37], although there is still an ongoing debate on this query [38]. In addition, detection of the *CRTC1-MAML2* fusion might be useful for diagnostic purposes since it is very characteristic of MEC, irrespective of anatomical location. Nevertheless, an identical fusion has also been identified in look-alikes of the so-called metaplastic Warthin tumor and in clear-cell hidradenomas of the skin [32, 39–41], thus broadening the spectrum of neoplasms associated with this gene fusion.

Recently, genomic studies have shown that fusion-positive MECs can be subdivided in low- and intermediate-grade tumors by copy number alterations [4, 6]. Tumors with no or only a few copy number alterations have a good prognosis, while tumors with numerous copy number alterations, including loss of the tumor suppressor *CDKN2A*, tend to be high-grade tumors and have a poor prognosis [7, 35, 36, 42]. It is noteworthy that there is a subgroup of tumors that may be classified morphologically as high-grade MEC but are negative for the fusion [6, 31, 35, 36]. Moreover, it has been speculated that at least some of the cases classified as high-grade tumors that do not carry the translocation might in fact not represent MEC but rather a more aggressive squamous carcinoma or a SDC [35, 36]. Irrespective of the *MAML2* fusion status, gene copy number alterations of either *HER2* or *EGFR* are associated with high- and extremely rarely low- and intermediate-grade MEC [10]. *HER2* or *EGFR* gene abnormality might play an important role in the development of high-grade MEC and also in the progression from *MAML2* fusion-positive low-/intermediate- to high-grade in a subset of MEC [10]. Whole-exome sequencing and gene copy number analyses performed on 18 MEC have shown that *TP53* is the most common mutated gene in MEC (28%). Interestingly, the mutations were only

found in intermediate- and high-grade MECs, and the mutated tumors had more mutations overall than tumors without *TP53* mutations ($p = 0.006$). The second most frequent mutated gene *POU6F2* was found in three low-grade MECs encoding the same in-frame deletion (187Q>-) [43]. The *POU6F2* gene encodes a member of the POU protein family; the family members are transcriptional regulators, many of which are known to control cell-type-specific differentiation pathways [44]. Loss of heterozygosity in regions containing *POU6F2* or overexpression of *POU6F2* has been reported in Wilms tumor [9, 45]. The authors proposed that beside the *CRTC1/CRTC3-MAML2* gene fusions as the main oncogenic driver, somatic *TP53* mutation may act as an alternate mechanism of tumorigenesis, and *POU6F2* mutations may act as drivers of oncogenesis in low-grade MEC [43].

In addition to *CRTC1/CRTC3-MAML2* fusions, rare cases with t(6;22)(p21;q12) translocation and *EWSR1-POU5F1* gene fusion have been reported [8]. Although these findings have been validated, analyses of larger tumor series are required to evaluate the diagnostic or biological significance of these findings. Last but not least, hotspot mutations in *HRAS* have been found in approximately 20% of MECs. The presence of *HRAS* mutations strongly correlates with high-grade tumor [46].

2.3 Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (AdCC) is one of the most common cancers of the salivary glands. It is composed of epithelial and myoepithelial neoplastic cells that form various patterns, including tubular, cribriform, and solid [1]. Although AdCC of the salivary gland is a slow-growing tumor, long-term prognosis is poor due to frequent local recurrences, distant metastases, and tendency for perineural invasion [1, 47].

Genomic studies of AdCC have shown that losses of 1p and 6q are associated with high-grade tumors and poor prognosis, whereas loss of 14q is exclusively seen in low-grade tumors [11, 48]. Key genomic alteration in AdCC is a recurrent t(6;9)(q22~23;p23~24) chromosomal translocation that results in a fusion of the transcription factor genes *MYB* and *NFIB* (Fig. 2.1) [49]. The *MYB* oncogene acts as a regulator of stem cells. The gene is highly expressed in immature, proliferating cells and is downregulated during differentiation [50]. *NFIB* encodes a transcription factor that controls cell proliferation and cell viability [19]. The MYB-NFIB fusions, which consist of the DNA binding and transactivation domains of MYB fused to different parts of the three-end of NFIB, interrupt the C-terminal part of MYB, leading to loss of negative regulatory sequence elements and, subsequently, to overexpression of the fusion protein [49]. 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 [48, 51, 52]. The latter events result in overexpression of a normal MYB protein, whereas the fusion events usually result in expression of truncated MYB proteins.

Recent molecular analyses, including whole-exome sequencing of AdCCs, have revealed a wide mutational diversity and low somatic mutation rate, with gene mutations influencing a wide variety of pathways, such as mutations

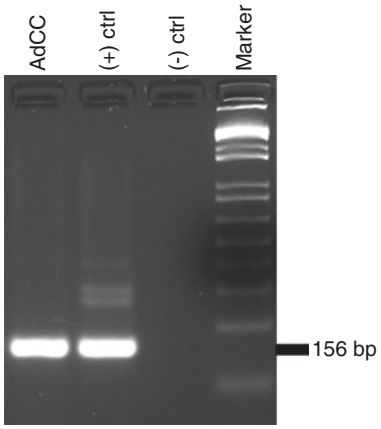

Fig. 2.1 AdCC carrying the *MYB-NFIB* gene fusion, detected by RT-PCR. (+) positive, (−) negative, ctrl control

affecting the FGF-IGF-PI3K pathway in 30% of samples as well as in the NOTCH1 pathway in 13% of the cases [12, 53]. Interestingly, *KIT* and *EGFR*, which are frequently overexpressed in AdCC, are rarely mutated or amplified. The translocation t(6;9) is the only highly recurrent genetic alteration in these tumors suggesting that the product of the *MYB-NFIB* fusion gene is a key driver mutation in the development of AdCC. In a subset of AdCC, t(8;9) and t(8;14) translocations are detected, fusing the *MYBL1* gene to *NFIB* and *RAD51B*, respectively [13, 54].

In summary, *MYB/MYBL1* activation due to gene fusion or other mechanisms occurs in the vast majority (60–80%) of AdCC and is a novel diagnostic biomarker for this tumor entity [13, 14, 55]. Also, its clinical application as new molecular target for therapy in AdCC patients is promising though functional studies are necessary.

2.4 Mammary Analogue Secretory Carcinoma

Certain types of SGCs have striking histological similarities with mammary tumors and indeed share overlap in molecular features. Mammary analogue secretory carcinoma (a.k.a. secretory carcinoma or MASC) is a newly described salivary gland carcinoma that is defined by its histologic, immunophenotypic, and genetic similarities to secretory breast carcinoma (SC) (Fig. 2.2a) [56, 57]. Key genomic alteration in both SC of the breast and MASC is the *ETV6-NTRK3* chimeric tyrosine kinase generated by a balanced chromosomal translocation t(12;15)(p13;q25) [56, 58]. The chromosomal alteration can be detected by *ETV6*-fluorescence in situ hybridization or by RT-PCR for the *ETV6-NTRK3* fusion transcript (Fig. 2.2b). The *ETV6-NTRK3* fusion can be found in the vast majority of MASC [56]. MASC typically has an indolent clinical course, although sporadic cases with high-grade transformation have been reported [59]. Further studies are needed to clarify whether the clinical behavior of MASC matches the tumor's low-grade histologic appearance. Before their initial description, these salivary gland tumors were generally diagnosed as ACC or adenocarcinoma, NOS.

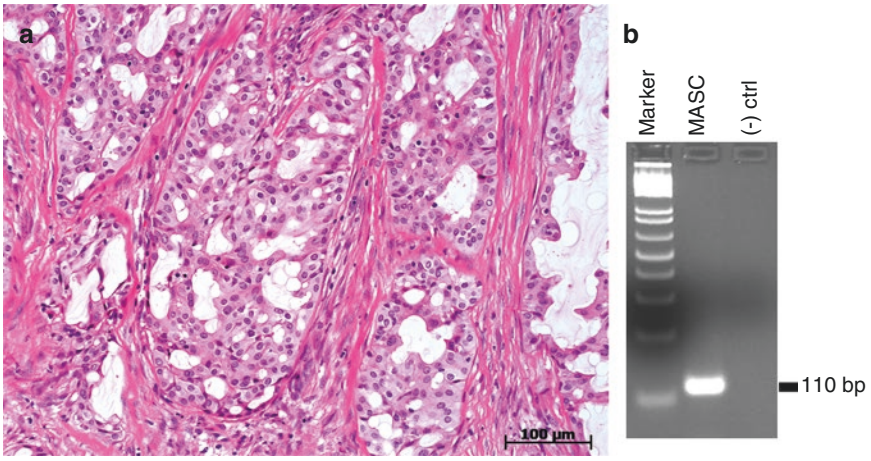

Fig. 2.2 (**a**) Typical MASC with partly confluent tumor complexes containing abundant (foamy) secretory material. The eosinophilic tumor cells are cuboidal in shape and contain moderately atypical nuclei. (**b**) MASC-specific *ETV6-NTRK3* gene fusion detected by RT-PCR. (−) negative, ctrl control

Expression of the *ETV6-NTRK3* gene fusion leads to constitutive activation of the Ras-MAPK and the PI3K-AKT pathways [15, 56, 58]. Recent studies have shown that a subset of fusion-negative MASCs have variant fusions involving *ETV6* and an unknown fusion partner, designated as *ETV6-X* fusions, and tumors with these fusions may behave more aggressively than *ETV6-NTRK3*-positive cases [16, 60]. The presence of the *ETV6-NTRK3* fusion gene has not been demonstrated in any other salivary gland tumor so far. Interestingly, the same t(12;15) translocation with the same fusion gene was also described in congenital mesoblastic nephroma [61], congenital fibrosarcoma [62], and some cases of myelogenous leukemia [63], indicating that this chimeric tyrosine kinase has transforming activity in multiple cell lineages. Studies that have identified MASCs retrospectively have demonstrated that they had previously most often been classified as ACC, MEC, or adenocarcinoma/cystadenocarcinoma, NOS [56, 64–68]. Taking into account the different tumor biology of these neoplasias, it is mandatory to exploit all immunohistochemical and molecular tools prior to the final diagnosis.

2.5 Hyalinizing Clear-Cell Carcinoma

Hyalinizing clear-cell carcinoma (a.k.a. clear-cell adenocarcinoma, clear-cell carcinoma, or HCCC) is a unique low-grade tumor with rare metastases and a very good prognosis. The tumor has a typical clear-cell morphology and pattern of hyalinization often with focal mucinous differentiation [1, 17, 69].

Recurrent t(12;22)(q13;q12) translocation consistent with *EWSR1-ATF1* gene fusion in HCCC has been described [70]. Rearrangements of *EWSR1* not only have been found in about 85% of HCCC [17, 18, 70] but also in a high percentage of

clear-cell odontogenic carcinomas (CCOC), suggesting a biologic link between these two malignancies [71]. In contrast, the fusion has not been detected in any of the morphological mimics: epithelial-myoepithelial carcinoma, myoepithelial carcinoma, or MEC, demonstrating its usefulness as a diagnostic biomarker for HCCC [70]. The translocation appears to be very specific to HCCC. Interestingly, high-grade transformation of HCCC with *EWSR1* rearrangement has been reported recently [72].

2.6 Carcinoma Ex Pleomorphic Adenoma

Carcinoma ex pleomorphic adenoma (CXPA) is defined as a carcinoma arising from a primary or recurrent benign pleomorphic adenoma (PA). It amounts to approximately 10–15% of all SGCs. The malignant component is frequently an adenocarcinoma, NOS, or SDC or may be any other histological subtype of SGC, such as MEC or AdCC (Fig. 2.3) [1]. CXPA is often a high-grade malignancy and especially when associated with deep (extracapsular) invasion has to be regarded as neoplasia with high risk of progression. High-grade adenocarcinoma, NOS, and

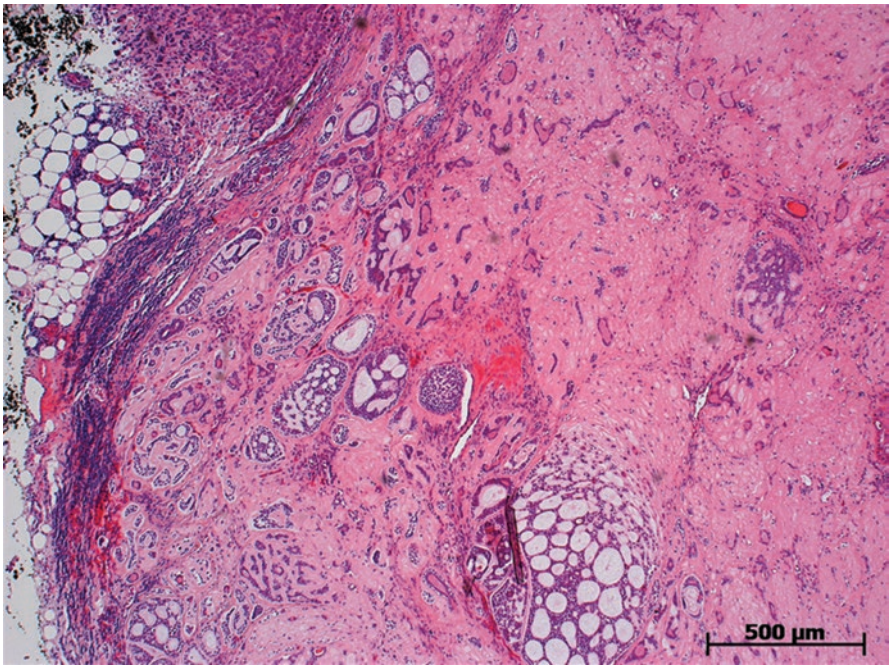

Fig. 2.3 H and E staining of CXPA. Tumor is partly encapsulated and shows residues of PA (right) with abortive ductal formation and dissociated myoepithelial cells in a sclerosing background. At the bottom of the figure and in the lower left part, several typical (pseudo-) cribriform manifestations of an AdCC. In addition, the upper left part shows invasion into the surrounding fatty tissues, the tumor component later classified as SDC (positive for AR and p53, data not shown)

SDC are the most common histologic subtypes, counting for approximately 80% of the carcinomatous components [1, 20]. However, some cases of CXPA are low-grade tumors, following a more indolent course [20]. The understanding of molecular mechanism causal for the transformation process of a benign PA into a CXPA is still very limited. Because of the tremendous diversity in histologic appearance, recent molecular studies have attempted to identify the genetic abnormalities that define this tumor. CXPA can express PA-specific gene fusions involving the transcription factor genes *PLAG1* (e.g., *CTNNB1-PLAG1*) and *HMGA2* (e.g., *HMGA2-WIF1*) [51, 73–76]. Subsets of CXPA also show amplification of *MDM2* and *HMGA2* in 12q13–15, mutations of *TP53* and/or amplification of *ERBB2* (HER2) as markers of malignant transformation [23, 73, 75, 77]. Most CXPA with *ERBB2* amplification are SDCs developing within PAs; these patients may benefit from treatment with trastuzumab [21].

2.7 Salivary Duct Carcinoma and Low-Grade Intraductal Carcinoma

Salivary duct carcinoma (a.k.a. high-grade ductal carcinoma or SDC) is one of the most aggressive malignancies of the salivary gland representing about 10% of all SGCs. Local recurrences as well as regional lymph node involvement and distant metastases are common. It can occur de novo or as the malignant component of CXPA and shows many genetic and histologic similarities to invasive ductal carcinoma of the breast [1, 78, 79]. Recent molecular analyses, including whole-exome sequencing, have revealed a wide mutational diversity and a high mutational burden (1.7 mutations/megabase) for SDC [80]. Frequently detected genetic alterations were mutations in *TP53* (55%), *HRAS* (23%), and *PIK3CA* (23%) and amplification of *ERBB2* (35%). The majority (74%) of tumors had alterations in either MAP-kinase genes (*BRAF/HRAS/NF1*) or *ERBB2* [80]. These results are in line with previous studies, which reported that the most common alterations in SDC are mutations in *TP53* (>50%), *PIK3CA* (~30%), *HRAS* (~30%), *BRAF* (7%), and *EGFR* gain (~80%), and loss, or mutation of *PTEN* (~40%) [81]. Additionally, more than 70% of SDCs have copy number gain and/or overexpression of the androgen receptor (*AR*) [79, 80, 82, 83]. Knockdown of AR expression in SDC cells in vitro markedly inhibits growth, suggesting that SDC patients with AR-positive tumors may benefit from androgen deprivation therapy [83]. Dalin and coworkers have emphasized the fact that the majority (61%) of SDCs have genetic alterations for which published clinical evidence supporting specific targeted therapies exists [80]. Taken together, the molecular data of SDC suggest that for this disease tumor sequencing on a routine basis is likely to be of clinical value.

There is also a very uncommon low-grade variant of SDC, with a favorable prognosis after complete excision. After a long discussion, the term low-grade SDC for these entities was replaced by low-grade intraductal carcinoma (a.k.a. low-grade cribriform cystadenocarcinoma, ductal carcinoma in situ, low-grade salivary duct carcinoma, or IDC), to clarify that these tumors are biologically different from

ordinary SDC [1, 84, 85]. These lesions are indolent but can be graded as low-, intermediate-, or high-grade tumors depending on the degree of the cytologic abnormalities present. Reported tumors have been described as typically small, unencapsulated, and cystic [85, 86]. In contrast to SDC, no amplification of *ERBB2* was found in low-grade IDCs [87]. Interestingly, approximately 13% of IDCs show focal transformations into a high-grade morphology [85, 86, 88]. However, the clinical impact of this transition is not clear, since the number of high-grade IDCs is very small and the median follow-up is only 27 months [84]. Nevertheless, there is indication that high-grade IDC have good prognosis [88].

2.8 Acinic Cell Carcinoma

Acinic cell carcinoma (ACC) is a low-grade, slow-growing tumor [1]. Histopathologically, variable architectural patterns have been described: solid, microcystic, papillary-cystic, and follicular [89]. Classifying ACC according to these subtypes can be challenging, as different patterns may occur in a single lesion [90]. Since the emergence of MASCs as a distinct tumor entity, the defining characteristics of ACC have come under question. New evidence suggests that it may be a far more aggressive tumor than originally reported [91]. As mentioned above, tumors previously classified as ACC were often retrospectively identified as MASC.

The knowledge of the associated molecular background is still very limited. Only in a minority of ACC, an abnormal karyotypic profile has been found, and the only common change observed was trisomy 8 in three cases [92]. No gene fusions or recurrent mutations have been identified so far. Studies on growth factor receptors using tissue microarrays with 168 ACCs have shown epidermal growth factor receptor (EGFR, HER1) immunoreactivity in 30 ACC (18%) [93] and overexpression of epidermal growth factor receptor 2 (ERBB2, HER2) in 1 single case out of 170 ACC (0.6%) [94]. However, in situ hybridization suggests overexpression of *ERBB2* on mRNA level in ACC [24]. Recently, it was shown that mice with constitutive activation of the Wnt and mTOR signaling pathways develop tumors that have remarkable morphologic similarity to human ACCs [25]. Treatment of tumor-bearing mice with the mTOR inhibitor rapamycin resulted in complete regression of the tumors. Immunohistochemical analysis of human ACC samples showed that mTOR signaling is also activated in human ACCs, indicating that mTOR inhibitors such as rapamycin or temsirolimus might be useful for treatment of patients with ACC [25, 95].

2.9 Polymorphous Adenocarcinoma and Cribriform Adenocarcinoma

Polymorphous adenocarcinoma (a.k.a. polymorphous low-grade adenocarcinoma, PLGA, or PAC) is a usually indolent low-grade salivary gland malignancy characterized by uniform cytology and histologic diversity [1]. Histopathologically, PAC is a challenging diagnosis. The two main differential diagnoses are AdCC and PA. The tumor occurs mainly at intraoral sites and sporadically in the major glands [1].

Cribriform adenocarcinoma of minor salivary glands (CAMSG) is a low-grade carcinoma, mainly found in the tongue and oropharynx, that shares morphologic, clinical, and molecular features with PAC [1, 22].

A variety of molecular and genetic findings have been reported in PAC lately. The majority of PACs (~75%) harbor somatic rearrangements of *PRKD1*, *PRKD2*, and *PRKD3* or somatic mutations of *PRKD1* encoding p.Glu710Asp, distinguishing them from other salivary malignancies [96, 97]. Thus, *PRKD1* mutations could be tested as a biomarker to distinguish PAC from its mimics. Interestingly, CAMSG has also alterations of *PRKD* family genes. *PRKD1* and *PRKD3* rearrangements were found in ~80% of CAMSG. In some cases recurrent *ARID1A-PRKD1* and *DDX3X-PRKD1* gene fusions were detected [97, 98]. These findings indicate a shared molecular pathogenesis for PAC and CAMSG. These facts raise the question whether PAC and CAMSG represent separate entities or variants of one spectrum [1, 97].

2.10 Conclusions

The discovery of specific and recurring translocations, point mutations, and amplifications in some types of SGC has given pathologists new and highly specific diagnostic tools and in some cases prognostic and possibly treatment-relevant markers. While diagnosis, i.e., confirmation of tumor-type and its related prognostic impact, may be supported in all tumors listed above, the detection of the MEC-related fusion gene and other molecular markers may provide segregation of tumors with low and high risk of progression. Also, the detection of fusion gene characteristic for certain SGC (particularly AdCC) may facilitate a tailored therapeutic approach in a multimodal setting, analogous to what is aimed for in the EORTC study 1206 for patients with SDC (see Chap. 13).

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