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Review Article

Systemic therapies for salivary gland adenoid cystic carcinoma

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Abstract: Adenoid cystic carcinoma (ACC) is a slow growing, but relentless cancer. Due to its rarity and lack of understanding of its molecular etiology, no standard chemotherapy for ACC currently exists and many patients suffer from recurrent and/or metastatic disease. As such, development of safe and effective therapies is imperative. To describe and summarize existing clinical trial studies and preclinical discoveries, we surveyed the PubMed on developmental therapeutics for ACC. Objective response rates to monotherapy with cytotoxic agents were approximately 10% with cisplatin, 5-FU, gemcitabine, mitoxantrone, epirubicin, vinorelbine and paclitaxel. The most studied combination therapies were cyclophosphamide-doxorubicin-cisplatin (CAP) and cisplatin-vinorelbine, with an objective response rate of 18-31%. Among molecularly targeted drugs, the most studied drugs are inhibitors targeting the vascular endothelial growth factor receptor (VEGFR) to inhibit tumor angiogenesis. Among those, lenvatinib and axitinib showed a relatively high objective response rate of 11-16% and 9-17%, respectively. Given high recurrence rates and chemoresistance of ACC, treatments targeting cancer stem cells (CSC), which function as tumor-initiating cells and drive chemoresistance, may be particularly valuable. CSC have been shown to be targetable via MYB, Notch1, p53 and epigenetic mechanisms. Myb overexpression is characteristic in ACC but was previously thought to present a difficult target due to its nature as a transcription factor. However, due to the development Myb-targeted inhibitors and an ongoing clinical trial of MYB-targeted cancer vaccine therapy, MYB is becoming an increasingly attractive therapeutic target. Drugs targeting NOTCH signaling demonstrated 5-17% response rate in phase I clinical trials. Within the field of epigenetics, treatment with PRMT5 inhibitors has shown 21% partial response rate in phase I clinical trial. Immunotherapies, such as PD-1 inhibitors, are also associated with CSC, but have not been effective against ACC. However, clinical trials of cancer vaccine therapies are actively being conducted. In addition to conventional chemotherapies and inhibitors of angiogenesis, the emergence of new therapies such as immunotherapy and those targeting cancer stemness is expected to bring clinical benefits to patients in the future.

Keywords: Adenoid cystic carcinoma, cancer stem cells, systemic therapy, chemotherapy, immunotherapy, salivary gland cancer

Introduction

Adenoid cystic carcinoma (ACC) is a relatively rare cancer, accounting for 1% of head and neck tumors and 10% of salivary gland tumors [1]. Salivary glands present the most common primary site for ACC, but tumors may also occur in the lacrimal glands, paranasal sinuses, mammary glands, skin, and genital organs [2-5]. The disease progresses relatively slowly, but continues to grow relentlessly, giving rise to a 5-year and 10-year patient survival rate of about 60% and 50%, respectively. Notably, the 20-year survival rate is only 20%, due to high incidences of recurrence and metastasis [6]. Lungs constitute the most common site for metastases, while perineural invasion is characteristic of local progression for ACC [7-9].

At present, the standard treatment for ACC remains surgery with or without radiation therapy, as no approved systemic therapy currently

exists. Although radiation therapy has a positive effect for local disease control, its effect on prolonging overall survival is unclear [10, 11]. Distant metastasis is the most common type of relapse, with about 30% of patients with distant metastasis not experiencing recurrence of the primary lesion [10, 12].

The need for a robust preclinical ACC model is apparent to advance basic and translational research within the field. However, it was reported that 6 types of ACC cell lines (ACC2, ACC3, ACCM, ACCNS, ACCS and CAC2) commonly used by many laboratories were cross-contaminated with other cells. This poses a large question mark on the research resulting from use of these cells, while leaving *in vitro* studies reliant on use of low passage primary cells [13]. Recently, Moskaluk and collaborators reported a xenograft model that reproduces the characteristics of human ACC [14], from which several cell lines have been established, thereby raising expectations that the understanding of pathological conditions underlying ACC will be accelerated [15]. More recently, a MYB-NFIB fusion-positive ACC cell line was developed and characterized as well suited for developmental therapeutics studies [16]. In this review, we will focus on the current state of pharmacological treatment of ACC. We surveyed the PubMed, summarized results of clinical trials, and discussed the potential clinical benefit of these therapies to ACC patients in the future.

Clinical trial data for cytotoxic chemotherapy

Single agent

In 10 studies focusing on single agent chemotherapeutic treatment, only 22 out of 163 (16%) patients demonstrated objective responses. No response was seen in the 21 patients who received gemcitabine or the 14 patients who received paclitaxel [17, 18]. Cisplatin and 5-FU showed relatively high objective response rates. Response rates to cisplatin vary widely from report to report, ranging from 0 to 70%. In addition, a 33% (4 of 12) objective response rate was observed upon 5-FU treatment [19-22]. Regarding the anthracycline cytotoxic agents mitoxantrone and epirubicin, the number of patients participating in the study was relatively large, whereas the objective response rate was only 5-12% [23-25] (**Table 1**). Almost half of patients showed stable disease (65 of 113). However, it was difficult to determine whether the disease was stable due to the drug's effect or the natural history of ACC.

Combination chemotherapy

The combination of cisplatin, doxorubicin and cyclophosphamide (CAP) was the most common regimen for ACC, sometimes combined with 5-FU. From 5 studies, 27% patients (12 of 43) presented objective responses [26-30]. Patients treated with a CAP plus 5-FU regimen demonstrated the longest duration of objective response. However, the authors mentioned that this treatment was too toxic to be considered standard treatment [30]. Cisplatin and doxorubicin were used in combination with bleomycin, in which 3 of 9 patients showed objective response [21]. The combination of cyclophosphamide, vincristine, and 5-FU showed a rather long duration of objective responses [31]. The above studies have been conducted relatively early. However, the regimens of paclitaxel-carboplatin and cisplatin-vinorelbine are newer and have been reported since 2000. Two studies investigated the combination of carboplatin with paclitaxel, where 2 of 10 and 1 of 9 patients showed objective responses [32, 33]. A randomized phase II trial was completed to compare single-agent vinorelbine with cisplatin plus vinorelbine, but included only 36 patients (of which 22 patients had ACC) [34]. Another study showed that 7 of 34 (20%) and 6 of 19 (31%) patients demonstrate objective responses [35, 36]. In several studies, the combination therapy groups demonstrated greater toxicities, particularly nausea, vomiting, myelosuppression, and neuropathy. Notably, the vinorelbine plus cisplatin regimen shows higher objective response rate compared to the response to the CAP regimen. Overall, when focusing on studies with 10 or more patients, the best objective response rates were obtained with cisplatin-vinorelbine combination [28, 29, 33, 35-37] (**Table 1**).

Targeted therapies

c-Kit and EGFR

As in many other cancers, treatment with molecularly targeted drugs has been attempted in ACC. It is known that high c-Kit expression

Table 1. Studies reporting cytotoxic chemotherapy for ACC

single agent	authors	year	# of patients with ACC	objective responses	duration	stable disease	median survival (months)
cisplatin	Schramm et al. [19]	1981	10	7 (70%)	7-18 months	NS	NS
	Licitra et al. [20]	1991	13	2 (15%)	5-8 months	6 (46%)	20
	Dick Haan et al. [21]	1992	10	0		5 (50%)	78
5-FU	Tannock et al. [22]	1980	12	4 (33%)	5-24 months	2 (17%)	NS
gemcitabine	van Herpen et al. [18]	2008	21	0		11 (52%)	NS
mitoxantrone	Verweij et al. [23]	1996	32	4 (12%)	3-13 months	22 (69%)	18
	Mattox et al. [24]	1990	18	1 (5%)		12 (66%)	19
epirubicin	Vermorken et al. [25]	1993	20	2 (10%)	7.5, 20 months	NS	16
vinorelvine	Airoldi et al. [34]	2001	13	2 (15%)	NS	NS	NS
paclitaxel	Gilbert et al. [17]	2006	14	0		7 (50%)	25
combination therapy							
CAP	Licitra et al. [29]	1996	12	3 (25%)	5, 9, 13 months	5 (41%)	34
	Creagan et al. [28]	1988	11	2 (18%)	12, 12 months	NS	22.5
	Belani et al. [26]	1988	4	1 (25%)	16 months	NS	13
	Dreyfuss et al. [27]	1987	9	3 (33%)	NS	NS	NS
CAP + 5-FU	Dimery et al. [30]	1990	7	3 (42%)	6, 13, 18 months	2 (28%)	29
P + A + bleomycin	Dick Haan et al. [21]	1992	9	3 (33%)	6, 21, 77 months	5 (55%)	67
CVF	Triozzi et al. [31]	1987	8	2 (25%)	107, 28 months	4 (50%)	NS
P + 5-FU	Hill et al. [37]	1997	11	0		9 (81%)	12
carboplatin, paclitaxel	Airoldi et al. [33]	2000	10	2 (20%)	5, 12 months	NS	NS
	Nakano et al. [32]	2016	9	1 (10%)	NS	NS	21.9
P + vinorelvine	Airoldi et al. [34]	2001	9	4 (44%)	NS	NS	NS
	Airoldi et al. [35]	2017	34	7 (20%)	NS	NS	10.2
	Hong et al. [36]	2018	19	6 (31%)	NS	10 (52%)	NS

*P: cisplatin, C: cyclophosphamide, A: doxorubicin, V: vincristine, F: 5-fluorouracil.

was confirmed in 90% of ACC tumors [38]. But, single drug imatinib (targets c-Kit) resulted in no objective responses in ACC [39-41]. Dasatinib, which also targets c-Kit, failed to show any activity in ACC [42]. In one trial, combination treatment with cisplatin and imatinib was conducted and showed 3 (10%) cases of partial response [43]. Increased expression of epidermal growth factor receptor (EGFR) was also observed in ACC [44]. However, clinical trials with EGFR inhibitors (*e.g.* cetuximab, gefitinib, lapatinib) did not provide a positive therapeutic responses [45-47] (**Table 2**). Given the results of these trials, molecular targets other than c-Kit and EGFR have been considered in ACC.

Targeting angiogenesis

Vascular endothelial growth factor (VEGF) is highly expressed in approximately 76% of ACC patients, raising the possibility that VEGF function may be associated with recurrence and metastases [48]. It has also been shown that overexpression of MYB promotes expression of several target genes including VEGF [49]. Therefore, VEGF receptor (VEGFR) could be considered as a potential therapeutic target for ACC. Chen and colleagues [50] have shown the efficacy of regorafenib in a preclinical study, where it led to delayed tumor growth and metastasis in 2 patient-derived xenograft (PDX) mouse models. To observe impacts of treatment of metastasis, they implanted labeled ACC cells in zebrafish embryos. Regorafenib treatment inhibited ACC cell migration and intravascular invasion as compared to the control group. Several VEGFR-targeted drugs are being tested in clinical trials. No objective response was observed to sunitinib, regorafenib, and nintedanib [51-53], but 9-16% objective response rate was observed with sorafenib, axitinib, and Lenvatinib. These data suggest limited efficacy of VEGFR-targeted treatment [54-59] (**Table 2**). Particularly, Tchekmedyian and collaborators showed that lenvatinib leads to the longest median progression-free survival (mPFS) of 17.5 months [55].

Table 2. Studies reporting targeted therapies for ACC

phase II studies	target	authors	year	# of patients	# of patients with ACC	objective responses	stable disease	median survival (months)	median PFS (months)
imatinib	c-kit, bcrabl, PDGFR	Hotte et al. [41]	2005	16	16	0	9 (56%)	7	2
		Pfeffer et al. [39]	2007	10	10	0	2 (20%)	NS	NS
		Bahl et al. [40]	2019	8	8	0	2 (25%)	NS	NS
imatinib + cisplatin		Ghosal et al. [43]	2011	28	28	3 (11%)	19 (67%)	35	15
dasatinib	c-kit, bcrabl, SRC family, PDGFβ, EPHA2	Wong et al. [42]	2016	54	40	1 (2.5%)	20 (50%)	14.5	4.8
cetuximab	EGFR	Locati et al. [46]	2009	30	23	0	20 (87%)	NS	NS
gefitinib	EGFR	Jakob et al. [45]	2015	36	19	0	13 (68%)	25.9	4.3
lapatinib	HER-2, EGFR	Agulnik et al. [47]	2007	40	19	0	15 (79%)	NS	3.5
dovitinib	FGFR, VEGFR, PDGFR, c-Kit	Keam et al. [68]	2015	32	32	1 (3%)	30 (93%)	NS	6
		Dillon et al. [69]	2017	34	34	2 (6%)	22 (65%)	20.6	8.2
sunitinib	VEGFR, c-KIT, PDGFR	Chau et al. [52]	2012	13	13	0	11 (85%)	18.7	7.2
regorafenib	VEGFR, FGFR, PDGFR	Ho et al. [51]	2017	38	38	0	17 (45%)	NS	NS
nintedanib	VEGFR, FGFR, PDGFR	Kim et al. [53]	2017	20	13	0	10 (77%)	10	7.9
lenvatinib	VEGFR, FGFR, PDGFR and etc.	Tchekmedyian et al. [55]	2019	32	32	5 (16%)	24 (75%)	NS	17.5
		Locati et al. [54]	2020	28	28	3 (11%)	20 (71%)	27	9.1
axitinib	VEGFR, PDGFR, c-KIT	Locati et al. [57]	2019	26	6	1 (17%)	3 (50%)	NS	NS
		Ho et al. [56]	2016	33	33	3 (9%)	25 (76%)	NS	5.7
sorafenib	VEGFR, PDGFR, c-Kit and etc.	Thomson et al. [58]	2015	23	23	2 (11%)	13 (57%)	19.6	11.3
		Locati et al. [59]	2016	37	19	2 (11%)	11 (58%)	26.4	8.9
vorinostat	histone deacetylase inhibitor	Goncalves et al. [114]	2017	30	30	2 (7%)	27 (90%)	11.5	10
everolimus	mTOR	Kim et al. [123]	2014	34	34	0	27 (79%)	NS	11.2
nelfinavir	Akt pathway inhibitor	Hoover et al. [124]	2015	15	15	0	7 (47%)	NS	5.5
phase I studies									
figitumab + dacomitinib	IGF1R + EGFR inhibitor	Calvo et al. [92]	2017	74	3	1 (33%)	2 (67%)		
R1507 + sorafenib	IGF1R + multikinase inhibitor	Mahadevan et al. [93]	2014		NS		1		
BMS-986115	pan-NOTCH inhibitor	Aung et al. [99]	2018	36	NS	0	2 (5.6%)		
crenigacestat (LY3039478) expansion of phase I	pan-NOTCH inhibitor	Even et al. [100]	2020	22	22	1 (5%)	15 (68%)	NS	5.3
brontictuzumab	NOTCH1 inhibitor	Ferrarotto et al. [101]	2018	48	12	2 (17%)	3 (25%)	NS	NS
GSK3326595	PRMT5 inhibitor	Siu et al. [119]	2019	44	14	3 (21%)	NS	NS	NS

Table 3. Ongoing clinical trials for ACC

ongoing phase II	Target or drug types	dose	clinical.gov
ATRA	retinoic acid receptor (RAR)	NS	NCT03999684
AL101	pan-NOTCH inhibitor	4 mg IV weekly	NCT03691207
CB-103	pan-NOTCH inhibitor	NS	NCT03422679
APG-115 ± carboplatin	MDM2-p53 interaction	150 mg every other day	NCT03781986
chidamide + cisplatin	histone deacetylase inhibitor	Chidamide: 30 mg orally two times per week, one week before cycle 1 treatment Cisplatin 25 mg/m^2 iv	NCT03639168
lenvatinib + pembrolizumab	VEGFR inhibitor + PD-1 antibody	Lenvatinib 20 mg daily, Pembrolizumab (200 mg)	NCT04209660
rivoceranib (apatinib)	VEGFR-2 inhibitor	oral rivoceranib, 700 mg daily	NCT04119453
ongoing phase I			
PRT543	PRMT5 inhibitor		NCT03886831
CV8102	intratumor therapy TLR7/8 agonist adjuvant		NCT03291002
VMD-928	TrkA inhibitor		NCT03556228
TetMYB Vaccine	cancer therapy vaccine with PD-1 antibody		NCT03287427

Currently, the VEGFR-2 inhibitor rivoceranib (apatinib) is in phase II trial (NCT04119453) (**Table 3**).

Tumor cells release VEGF and other pro-angiogenic factors to promote angiogenesis which enables influx of oxygen and nutrients to support the high metabolic demands of tumor growth. Interestingly, VEGF induces B-cell lymphoma (Bcl)-2 expression and enhances both endothelial and tumor cell viability in several tumor types [60]. The anti-apoptotic Bcl-2 and Bcl-x_L proteins are overexpressed in adenoid cystic carcinomas [61]. Acasigua and colleagues [62] showed the effect of a BH3-mimetic small molecule inhibitor (BM-1197) on ACC tumor suppression, where they demonstrated that small molecule inhibitors of Bcl-2 induce apoptosis of tumor cells by suppressing the heterodimerization of Bcl-2 and Bcl-x. In a PDX model of ACC, the BM-1197-treated group showed an increase in apoptotic rate and growth inhibition as compared to the control group. However, clinical studies targeting Bcl-2 have not been conducted yet for ACC.

Overexpression of fibroblast growth factor (FGF) has been observed in salivary gland cancers including ACC [63]. Increased FGF, as well as VEGF, has been shown to be associated with overexpression of MYB [64]. FGF is also involved in angiogenesis by promoting proliferation and migration of vascular endothelial cells [65]. Doddapaneni and colleagues reported responses of ACC of the lacrimal gland in protein expression due to intra-arterial cytoreductive chemotherapy (IACC) with cisplatin and doxorubicin. According to the study, immunofluorescence and immunohistochemical analyses demonstrate a significant increase of FGFR1 in post-IACC tissues, when comparing to pre-IACC. They also performed an *in vitro* study on ACC cells using cisplatin and AZD4547, a FGFR1 inhibitor. The cells treated with the FGFR1 inhibitor and cisplatin showed a lower cell proliferation rate and cell migration compare to the control group or the cisplatin alone group [66].

The clinical trial for dovitinib is one of the trials targeting FGFR in ACC. Dovitinib is also a drug that targets VEGFR, but it has a higher affinity for FGFR when compared to sorafenib and lenvatinib [67]. In the phase II clinical study on dovitinib, the objective response rate was 3-6%, which was lower than that of Lenvatinib [68, 69].

Targeting stemness

Cancer stem cells in adenoid cystic carcinoma

Cancer Stem Cells (CSCs) constitute a small fraction of the entire tumor cell population (typically ≥5%). These cells are highly tumorigenic, capable of self-renewal, and capable of (re-) generating the various cell phenotypes that make up a tumor [70]. It has been suggested that CSCs are resistant to conventional chemotherapy and are strongly associated with recurrence and metastasis [71, 72]. Methods for identifying CSCs have been suggested in various types of carcinoma, and the markers identified for labeling differ depending on the type of carcinoma. In a study using a PDX model of ACC, when $ALDH^{high}$ and $ALDH^{low}$ cell

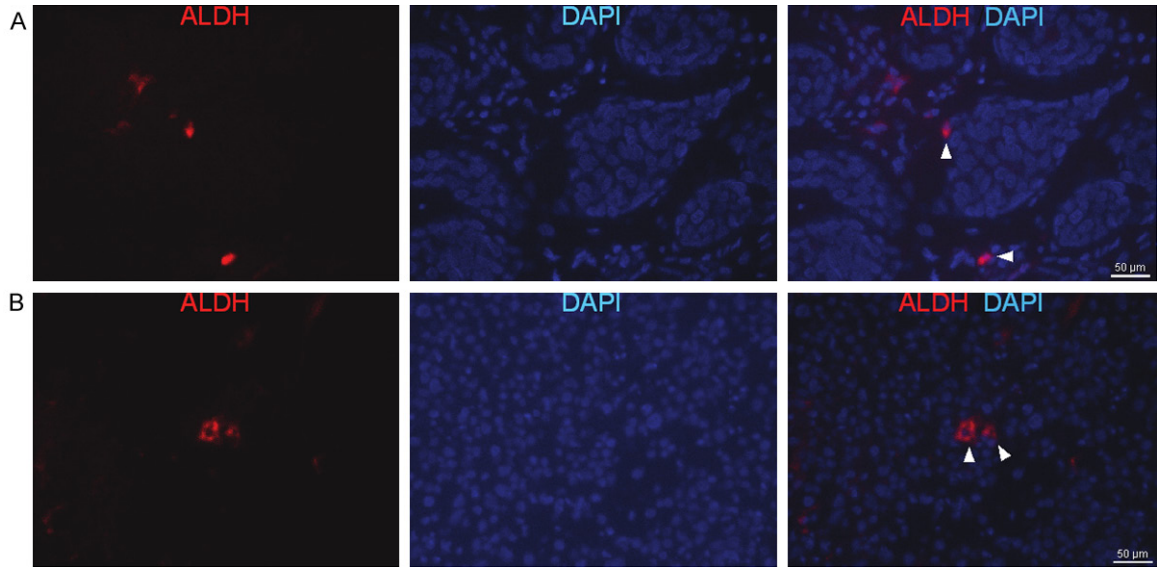

Figure 1. Representative photomicrographs of immunofluorescence staining of putative cancer stem-like cells in Adenoid Cystic Carcinoma. Histological section prepared from a surgical specimen of human ACC (A) and from a patient-derived xenograft UM-PDX-HACC-5 (B). Tissues were stained for the CSC marker ALDH (red) and for DAPI (blue). Images were taken at 400× magnification. Scale bars represent 50 µm.

populations were subcutaneously injected into mice, $ALDH^{high}$ cell populations were capable of forming tumors with a smaller number of cells than $ALDH^{low}$ cells. This suggested that $ALDH^{high}$ cells have high tumorigenicity, and that ALDH is an effective CSC marker in ACC [73] (**Figure 1**). In another study, when the $ALDH^{high}CD44^{high}$ and $ALDH^{low}CD44^{low}$ cells were compared for tumorigenicity, the $ALDH^{high}$ $CD44^{high}$ cells were more tumorigenic. From this, it was suggested that CD44 in addition to ALDH can be a marker for CSCs in ACC [74]. It has further been reported that CD44 and CD133 have overlapping expression in ACC, suggesting that CD133 may also serve as a marker to identify ACC CSCs [75].

As mentioned above, CSCs selected by the aforementioned markers constitute a very small population [74]. As such, an effective treatment targeting CSCs might eliminate this small cell population but would not result in immediate tumor regression. Thus, treatments targeting CSCs are typically accompanied by strategies (*e.g.* cytotoxic therapies) aiming at the elimination of bulk tumor cells [72]. Importantly, CSC-targeted treatment has the potential to reduce ACC recurrence rates, as it eliminates tumor-initiating cells. In a preclinical recurrence study using PDX models of ACC, inhibition of the MDM2-p53 interaction with a small molecule inhibitor reduced the fraction of CSCs and enhanced sensitivity to cisplatin. In addition, no tumor recurrence was observed after tumor resection in neoadjuvant administration of the targeted therapy group (MI-773), whereas 63% of the vehicle control group showed recurrence [76]. Altogether, treatment targeting CSCs can potentially be beneficial in ACC, as tumor recurrence is frequently observed.

MYB as a stemness target

A recurrent t(6;9)(q22-23; p23-24) translocation is a common chromosomal abnormality in ACC and results in the fusion of the proto-oncogene (MYB) with the transcriptional factor gene (NFIB) [49]. The MYB-NFIB gene fusion is observed in about 50% of all ACC tumors. Interestingly, 35% of MYB-NFIB gene fusion negative ACC have MYBL1 gene alterations. Therefore, it is suggested that approximately 80% of all ACC have MYB or MYBL1 gene alterations, and that MYB-like signaling might be involved in the oncogenesis and maintenance of ACC [77]. In tumors with MYB-NFIB translocation, the fusion is detected in all tumor cells. However, the expression of Myb protein is detected only in limited subsets of ACC cells, primarily with a basal phenotype. In the tumor cells with a basal phenotype, p63 has been

suggested as a CSC marker [78] and is typically co-expressed with Myb [79]. In addition, sphere formation in ultra-low attachment plates (functional *in vitro* assessment of stemness) was suppressed by MYB gene silencing. This suggests that MYB promotes tumorigenesis by enhancing cancer stemness [80].

Since MYB is a transcription factor, this genetic abnormality is particularly difficult to target clinically. However, initial approaches to inhibit MYB activity or expression by small molecule or peptide-mimetic inhibitors have already proven successful and have shown that MYB inhibition is feasible clinically. The main strategy to inhibit MYB remains targeting MYB's interaction with partner proteins or inducing direct degradation of MYB. CBP/p300 was the first identified coactivator to interact with Myb and influence its transcriptional activity [81, 82]. Recent studies have proposed that Celastrol, a natural low-molecular-weight compound, can inhibit MYB function through disruption of its interaction with the KIX domain of p300/CBP [83]. However, Celastrol reduced viability not only of MYB-positive ACC cells but also of cells not associated with MYB activation at the same concentration [84]. This suggests that Celastrol inhibits non-selective cell viability. To improve the therapeutic specificity for MYB, a peptidomimetic inhibitor (MYBMIM) that was designed to target and interfere with the assembly of the MYB:CBP/P300 co-transcriptional protein complex using structure-guided molecular design was utilized [85]. A dose-dependent tumor cell viability reduction was observed in MYB-activated tumor cells by MYBMIM. On the other hand, incubating MYBMIM with cells that are not associated with MYB activation does not decrease cell viability. This suggests that MYBMIM may be a viable selective MYB inhibitor for the treatment of ACC patients [84]. Yusenko and colleagues showed that the polyether ionophore monensin A (referred to monensin) has an inhibitory effect on MYB and induces its degradation *in vitro*. Using MYB-NFIB mutation-positive ACC cells, the expression of MYB was suppressed under the administration of monensin. Under similar conditions, the expression of VEGF, which is typically induced by MYB, was also suppressed [86].

One drug already in clinical use has been shown to have an inhibitory effect on MYB. Mandelbaum and collaborators demonstrated that All-trans Retinoic Acid (ATRA), clinically available for treatment of acute promyelocytic leukemia (APL), decreases c-MYB expression in myeloid leukemia cell via retinoic acid receptor (RAR). In a PDX model of MYB translocation-positive ACC, it was shown that ATRA and retinoic acid agonist suppresses tumor growth. They also examined apoptosis (cleaved caspase-3) and proliferation (Ki-67) in ACC xenograft tumors, and observed that ATRA treatment induced tumor cell death, but had no significant effect on tumor cell proliferation [87]. To verify these results in humans, a phase II trial of ATRA in Advanced Adenoid Cystic Carcinoma (NCT03999684) has been initiated (**Table 3**).

Immunomodulatory therapy to target MYB is another area of ongoing research. The TetMYB vaccine is a DNA vaccine targeting MYB. It was generated using a full-length MYB complementary DNA (cDNA) bound by two potent CD-4 epitopes derived from the tetanus toxin, which was then cloned into the FDA-compliant DNA vaccine vector pVAX1 [88]. Following several studies demonstrating that the TetMYB vaccine has a tumor suppressing effect for colorectal cancer [89, 90], a phase I clinical trial for colorectal carcinoma or adenoid cystic carcinoma is currently active [91] (NCT03287427) (**Table 3**).

Lastly, MYB has also been reported to be downregulated by inhibiting IGF1R signaling. In MYB-NFIB fusion-positive ACC cells, IGFR1/EGFR/MET are consistently activated. These receptors stimulate proliferation of ACC cells through AKT signaling. Inhibition of these signaling events upon treatment with linsitinib, crizotinib, or gefitinib (IGF1R/INSR, MET, and EGFR inhibitors, respectively) significantly decreased tumor growth in ACC xenograft models [80]. Currently, there are two phase I clinical trials IGF1R targeting. One trial tests figitumab combined with the EGFR inhibitor dacomitinib, and the another uses R1507 combined with sorafenib. In those studies, 1 patient with partial response for 1.5 years and 3 patients with stable disease were observed. Although clinical development of figitumumab has been discontinued, these clinical studies support that IGF1R signaling has the potential to inhibit ACC growth and progression [92, 93] (**Table 2**).

NOTCH1 as a stemness target

NOTCH signaling is an evolutionarily conserved cell fate determinant pathway that regulates stem cells in many adult tissues, as well as in pathological conditions such as cancer [94]. More recent data have established a correlation between NOTCH1 signaling and cancer stemness. Higher expression of NOTCH1 was observed in $CD133^+$ cells when compared to $CD133^-$ and unsorted cells. Silencing of NOTCH1 suppresses spheroid formation in low attachment culture conditions [95]. NOTCH1 signaling was also shown to indicate poor patient prognosis. NOTCH1 mutation leads to its activation as demonstrated by a luciferase reporter assay bearing the promoter of HES1, which is a Notch1 transcriptional target. The NOTCH1 mutation was found in approximately 13-14% of ACC patients [9, 96]. Patients harboring NOTCH1 mutations showed more aggressive histologies with a solid subtype, shorter relapse-free survival, and shorter overall survival when compared with NOTCH1 wild-type tumors. Although distant metastases with organ involvement outside the lungs predicted poorer outcomes [97], patients with NOTCH1 mutation exhibited a higher likelihood of developing metastasis in the liver and/or bone [9].

The NOTCH-pathway can be targeted with pan-notch inhibitors such as gamma-secretase inhibitors or Notch1 inhibitors. Preclinical studies demonstrated significant activity of Notch inhibitors (*e.g.* brontictuzumab, Notch1 inhibitor; AL101, pan-Notch inhibitor) in a NOTCH1 mutant ACC PDX. In both studies, brontictuzumab and AL101 had no significant effect on tumors lacking Notch1 activating mutations. For AL101, together with cisplatin or everolimus (mTOR inhibitor) was also studied, but this combination therapy had no additional benefit in Notch1 mutation-positive tumors [9, 98]. These preclinical studies suggested that when treating patients with Notch inhibitors, it may be more effective to select and treat patients who exhibit NOTCH1 mutations. There is some emerging data showing that Notch inhibitors benefit ACC patients. In a phase I study of BMS-986115 (pan-NOTCH inhibitor), some clinical benefits including 2 stable disease (SD) patients with ACC were shown. However, the study was terminated early [99]. In an expansion of a phase I study on crenigacestat (pan-Notch-inhibitor), a cohort of 22 ACC patients was enrolled. From this cohort, 14 (64%) patients were positive for Notch by immunohistochemistry, but mutation status was not given. In the trial, 1 patient had an unconfirmed partial response (PR) (15%) while 15 patients showed SD [100] (**Table 2**). Treatment using brontictuzumab also demonstrated clinical benefit with 2 PR patients and 3 SD patients out of 12 patients enrolled in a phase I trial. Bronticutuzumab (specific Notch1 inhibitor), was expected to reduce systemic toxicity (*e.g.* diarrhea) related to Notch inhibition in the intestinal crypts. However, the frequency and grade of diarrhea was comparable with that reported with other pan-Notch inhibitors [101]. Currently, one phase II clinical trial with AL101 (Gamma Secretase Inhibitor) is recruiting ACC patients with NOTCH1 mutation (NCT03691207), and another phase I/IIA study with CB-103 (targeting assembly of the NOTCH transcription complex in the cell nucleus) is recruiting patients with advanced or metastatic solid tumors including ACC (NCT03422679) [102] (**Table 3**).

p53 as a stemness target

Mutations in the TP53 gene are the most frequently found in human cancer. Indeed, p53 is known as the “guardian of the genome” playing a key role in the determination of cell fate. Under normal conditions, p53 is under tight molecular regulation. However, once the gene is mutated, it is released from the degradation mechanism of p53 and accumulates rapidly in the cell to promote various transcription factors involved in senescence and apoptosis. Mouse double minute 2 (MDM2) is a major negative regulator of p53 that promotes degradation of p53 upon direct binding [103]. It is considered that malignant tumors survive because p53 itself does not have proper function due to an abnormality in itself or an abnormality in the binding to MDM2 [104].

There is some relationship between p53 and CSCs regarding stem cell self-renewal and differentiation [105]. In studies with mammary stem cells, p53 deficiency increased self-renewal capacity, increased the stem cell pool, and promoted symmetric division of cells. p53 knockout mice were found to have a higher proportion of cells capable of generating mam-

mospheres, supporting the concept that p53 plays an important role in the generation and maintenance of the cancer stem cell pool [106, 107]. In addition, p53 promotes differentiation by suppressing the expression of Nanog in mouse embryonic stem cells [108]. Given these findings, it is concluded that p53 controls the balance between self-renewal and differentiation of stem cells.

Although TP53 is mutated in many cancers, it is not as frequently mutated in salivary gland tumors when compared to other neoplasms [109]. In addition, high expression of p53 was noted in 19 out of 21 ACC cases (90%) via immunohistochemistry [61]. This indicates that increased accumulations of p53 might have a therapeutic effect within ACC. In fact, inhibition of the MDM2-p53 interaction with small molecule (MI-773) activates downstream effectors of apoptosis and causes tumor regression in PDX models of ACC [110]. MI-773 also sensitized ACC PDX tumors to cisplatin and successfully reduced the fraction of CSCs ($ALDH^{high}$ $CD44^{high}$ cancer cells). Furthermore, inhibition of MDM2-p53 prevented tumor recurrence in preclinical trials. No recurrence was observed upon tumor resection after neoadjuvant administration of MI-773, whereas 63% of the mice in the control group showed recurrence [76]. Given these results, a Phase I/II trial of APG-115 (small molecule inhibitor of MDM2-p53) in patients with salivary gland tumors including ACC (NCT03781986) is currently ongoing (**Table 3**).

The epigenome as a stemness target

Treatments targeting the epigenome have been studied in many carcinomas, with ACC being no exception. Mutations related to the epigenome such as histone acetylation and methylation, as well as chromatin remodeling have been reported [111]. CBP/P300 described in MYB also has a histone acetyltransferase (HAT) function to acetylate H3K18 and H3K27 [112]. Histone deacetylase (HDAC), which has the opposite effect to HAT, has been shown to have an effect as a pro-oncogene [111]. A preclinical study showed that Vorinostat, an HDAC inhibitor (HDACi), has an effect of depressing CSC in ACC. In an *in vitro* study, Vorinostat reduced CSCs as identified by CD44 expression and ALDH activity in primary ACC cells. Furthermore, combination treatment with cisplatin reduced the CSC fraction when compared with Vorinostat monotherapy. From these data, it was shown that Vorinostat demonstrates not only the tumor suppressive effect of a single agent but also the effect of sensitizing cells to cisplatin [113]. Vorinostat has also been tested in clinical trial. In a phase II study in which 90% (27/30) of the patients exhibited disease progression prior to enrollment, there were 2 patients out of 30 (7%) with PR and 27 patients with SD [114] (**Table 2**). Although the PR rate was inferior when compared with anti-VEGFR drugs such as Lenvatiniv, considering the results of preclinical studies, it is possible that the combination treatment with conventional chemotherapy may be effective. To answer this question, another phase II trial of combination therapy with HDACi (chidamide, orally active histone deacetylase inhibitor) and cisplatin is being conducted (NCT03639168) (**Table 3**). Chidamide has been approved for the treatment of relapsed and refractory peripheral T-cell lymphoma and is expected to have a tumor suppressing effect on various types of carcinoma [115].

The inhibitor of the protein arginine methyltransferase 5 (PRMT5) may also have a therapeutic effect in ACC. PRMTs are involved in various signal transduction cascades by catalyzing methylation of specific arginine residues. Overexpression of PRMT5 has been confirmed in many carcinomas and is thought to have a role in cancer progression by inhibiting tumor suppressor gene expression via methylation of transcription factors and chromatin associated proteins [116]. In oropharyngeal cancers, high expression of PRMT5 in the nucleus indicates poor prognosis. Notably, and it has been shown that IL-6 promotes PRMT5 translocation into the nucleus [117]. In breast cancer, PRMT5 was overexpressed in chemoresistant cell lines compared to non-resistant cell lines. Conversely, it was observed that knocking down PRMT5 enhances drug sensitivity. In addition, PRMT5 knockdown inhibits sphere formation and decreases the CSC fraction identified as $CD44^{+}CD22^{-}$ [118]. Therefore, it is likely that PRMT5 has an association with carcinogenesis and cancer stemness. Preclinical studies showing a relationship between salivary gland carcinoma and PRMT5 are inadequate, but clinical trials have shown some

promise for ACC. Although it is an intermediate result of a Phase I trial, PR was confirmed in 3 out of 14 patients in the ACC patient group treated with GSK3326595, which is a PRMT5 inhibitors [119] (NCT02783300) (**Table 2**). In addition, another PRMT5 inhibitor (*i.e.* PRT543) is also undergoing phase I studies in patients with ACC (NCT03886831) (**Table 3**).

PI3K/Akt/mTOR pathway as a stemness target

Phosphatidylinositol 3-kinase (PI3K) activates Akt by phosphorylation. Furthermore, it activates transcriptional factors such as mammalian target of rapamycin (mTOR), an Akt substrate. Inhibition of mTOR has been shown to decrease expression of CSC markers and inhibit sphere formation in various cancer types including breast cancer and colorectal cancer. This indicates that inhibition of mTOR has a suppressive effect on CSCs [120]. In ACC, p-Akt is overexpressed when compared to normal salivary gland tissue, and therefore it may play a role in ACC carcinogenesis [121, 122]. However, high p-Akt expression was associated with lower grade histology, and it was even found that the p-Akt high-expressing group had a better prognosis [122]. In a phase II study of the mTOR inhibitor everolimus, 27 of 34 (79%) had SD, but no PR was seen [123]. Of note, nelfinavir (anti-HIV drug) has a tumor-suppressing effect by inhibiting Akt. As such, a phase II trial of nelfinavir was conducted in ACC, but only 7 out of 15 (46%) patients showed SD, none showed PR, and clinical prognosis was not affected [124] (**Table 2**).

Immunotherapy and cancer stemness

It is known that cancer cells can be eliminated by immune cells, creating a surveillance by the immune system that can inhibit tumor formation. However, tumorigenic cells might evade the immune surveillance and grow into tumors. CSCs are known to be able to evade immunological recognition and to exhibit tumorigenic potential. Immunosuppressive mechanisms have been characterized as key for tumor generation and progression, including programmed cell death 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), transforming growth factor β (TGF-β) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [125]. Therapeutic efficacy of PD-1/PDL-1 inhibitors has been demonstrated in head and neck squamous cell carcinoma (HNSCC), with higher levels of PD-L1 expressed in the $CD44^{high}$ CSCs group [126]. However, the therapeutic potential of inhibiting the PD-1/PD-L1 pathway in ACC remains unclear. A clinical trial of pembrolizumab (PD-1 inhibitor) was conducted, but no objective response was observed in ACC patients [127]. A combination of pembrolizumab and radiotherapy did not result in tumor regression [128]. Even with the combination therapy of vorinostat and pembrolizumab, the therapeutic effect was 8% (1 out of 12) in ACC, and no additional therapeutic effect for pembrolizumab was observed [129]. A potential reason for the lack of response to PD-1 inhibition might be because PD-L1 is rarely expressed in ACC and tumor-infiltrating lymphocytes (TILs) [130, 131]. Further, expression of PD-L2 alone was shown to aid in evasion of immune surveillance mechanisms [132]. PD-L2 expression tends to be relatively high in ACC [130, 131].

Emerging evidence suggests the possibility of developing anti-CSC vaccines. Cancer therapeutic vaccines activate a number of tumor antigen-specific cytotoxic T lymphocytes (CTLs) to eliminate the tumor by recognizing tumor-associated antigens [125]. Studies using the xenograft model of ovarian cancer have shown that the $CD117^{+}CD44^{+}$ CSC vaccine inhibits tumorigenicity [133]. A clinical trial of a MYB-targeted vaccine is being conducted in MYB-expressing tumors, such as ACC and colorectal cancer [91]. The results of this trial should shed light on the therapeutic potential of this new treatment modality.

Ongoing clinical trials

Intra-tumor therapy

When discussing immunotherapy, we mentioned anti-cancer vaccines. But vaccines using tumor-associated antigens may not elicit enough immunostimulatory action to evoke a sufficient immune response, which is required to have a strong and persistent tumoricidal effect. Most adjuvants have been developed for prophylactic vaccines and have a low Th1-activating effect. However, CV8102, a non-coding, long-chain RNA molecule, is an adjuvant that stimulates TLR7/8 and induces a robust

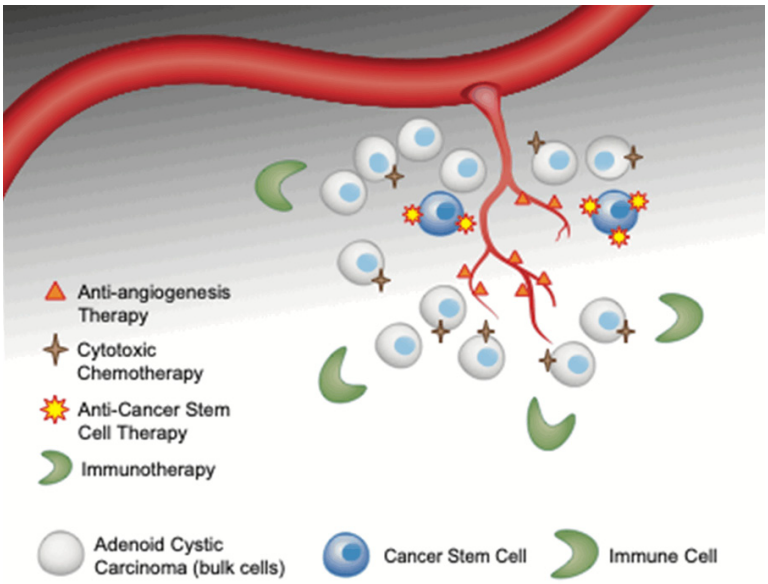

Figure 2. Graphical illustration depicting cytotoxic chemotherapy, anti-angiogenic therapy, stemness-targeted therapy and immunotherapy as potential strategies for treatment of therapy Adenoid Cystic Carcinoma.

immune response [134, 135]. In a preclinical study using an HPV-related cervical cancer model, comparing the vaccine containing HPV-16 E7 protein-derived long peptides alone with the vaccine and CV8102 together, the combination group showed a longer and more potent anti-tumor effect. It also demonstrated a stronger immunostimulatory effect than the existing adjuvant, *i.e.* poly (I:C) [136]. Furthermore, it has been reported that intra-tumoral administration of adjuvants alone has an anti-tumor effect by presenting the tumor cell itself as an antigen to immune cells [137]. Intra-tumoral administration of adjuvants also showed increased activation of immune evasion mechanisms such as PD-L1. Therefore, it has been suggested that combination with PD-L1 inhibitors may enhance antitumor effects [138]. Based on this evidence, a clinical trial exploring a combination therapy that includes intra-tumoral administration of CV8102 and PD-1 inhibitor for solid tumors including ACC is ongoing (NCT03291002) (**Table 3**). In the mid-term report, complete regression was confirmed in one patient with melanoma, and tumor shrinkage was observed in one patient with head and neck squamous cell carcinoma and another in a patient with melanoma [139]. Considering the potential immunostimulatory effect, combination therapies involving anti-cancer vaccines may become a novel strategy for ACC.

TRKA

Perineural invasion, a characteristic invasion pattern of ACC, poses a major challenge in the treatment of patients with ACC [140]. Neural invasion is also a prognosis factor of local control rate [141]. It is believed that neural invasion is associated with nerve growth factor (NGF) and its receptor Tropomysin receptor kinase A (TrkA). In ACC, high expression of NGF and TrkA displays significant correlation with neural invasion and disseminated disease [142, 143]. A Phase I study of oral small-molecule TrkA inhibitor has been conducted in many carcinomas including ACC is actively recruiting patients at this time (NCT03556228) [144] (**Table 3**).

Combination therapy

The observation that vorinostat enhanced the effect of cisplatin in preclinical studies [113], suggests that this drug combination may be effective in salivary gland cancer. The combination of either conventional chemotherapy with targeted therapies, or the combination of a molecular targeting drug with immunotherapy, are being actively pursued in clinical trials. The former is presented by combination therapies using HDACi and cisplatin (NCT03639-168), as well as APG-115 and carboplatin (NCT03781986), while the latter is presented by a combination therapy using lenvatinib and pembrolizumab (NCT04209660) (**Table 3**).

Conclusion

ACC is a rare disease found primarily in the salivary glands. Initial treatment for ACC is often surgery with or without radiation therapy, but most patients eventually experience tumor recurrence and/or metastasis. Chemotherapy is administered to control advanced, unresectable, recurrent and/or metastatic ACC, but a standard-of-care chemotherapy protocol is yet

to be determined. Although inhibitors of tumor angiogenesis demonstrated relatively high effective response rates, they were at best comparable to conventional chemotherapy in patients with ACC. However, NOTCH signaling inhibitors and PRMT5 inhibitors have higher efficacy response rates and show promise as putative therapeutic targets in ACC. Furthermore, clinical studies are being conducted on cancer vaccines targeting MYB and small molecule inhibitors of the p53-MDM2-p53 interaction. In addition, the emergence of new therapies targeting stemness and the maturation of immunotherapy protocols is expected to bring benefits to clinical patients in the future (**Figure 2**). The recent development of validated ACC cell lines and preclinical models that are suitable for developmental therapeutics studies, raise the speed of discovery and should enable discoveries towards safer and more effective therapies for ACC patients.

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Disclosure of conflict of interest

None.

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