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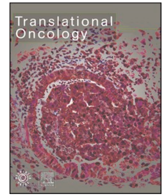

The imminent role of microRNAs in salivary adenoid cystic carcinoma

Pawan Kumar [1], Ram Kumar Kumawat [1], Vivek Uttam, Alisha Behera, Medha Rani, Neha Singh, Tushar Singh Barwal, Uttam Sharma, Aklank Jain [*]

Department of Zoology, Central University of Punjab, Ghudda, Bathinda, Punjab 151401, India

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ABSTRACT

Unfortunately, despite the severe problem associated with salivary adenoid cystic carcinoma (SACC), it has not been studied in detail yet. Therefore, the time has come to understand the oncogenic cause of SACC and find the correct molecular markers for diagnosis, prognosis, and therapeutic target to tame this disease. Recently, we and others have suggested that non-coding RNAs, specifically microRNAs and long non-coding RNAs, can be ideal biomarkers for cancer(s) diagnosis and progression. Herein, we have shown that various miRNAs, like miR-155, miR-103a-3p, miR-21, and miR-130a increase the oncogenesis process, whereas some miRNAs such as miR-140-5p, miR-150, miR-375, miR-181a, miR-98, miR-125a-5p, miR-582-5p, miR-144-3p, miR-320a, miR-187 and miR-101-3p, miR-143-3p inhibit the salivary adenoid cystic carcinoma progression. Furthermore, we have found that miRNAs also target many vital genes and pathways like mitogen-activated protein kinases-snail family transcriptional repressor 2 (MAPK-Snai2), p38/JNK/ERK, forkhead box C1 protein (FOXC1), mammalian target of rapamycin (mTOR), integrin subunit beta 3 (ITGB3), epidermal growth factor receptor (EGFR)/NF-κB, programmed cell death protein 4 (PDCD4), signal transducer and activator of transcription 3 (STAT3), neuroblastoma RAS (N-RAS), phosphatidylinositol-3-kinase (PI3K)/Akt, MEK/ERK, ubiquitin-like modifier activating enzyme 2 (UBA2), tumor protein D52 (TPD52) which play a crucial role in the regulation of salivary adenoid cystic carcinoma. Therefore, we believe that knowledge from this manuscript will help us find the pathogenesis process in salivary adenoid cystic carcinoma and could also give us better biomarkers of diagnosis and prognosis of the disease.

Introduction

Salivary adenoid cystic carcinoma (SACC) is a rare type of adenoid cystic carcinoma that mainly occurs in the salivary duct of patients and accounts for 28% of all salivary gland tumors [1]. Worldwide, it has an incidence rate of 4.5 cases per 1,00,000 population [2–5] and is characterized by distant metastasis, local infiltration, a higher recurrence rate, and poor prognosis [6]. Moreover, SACC progresses slowly in the early phase but becomes very aggressive in later stages. These characteristics lead to the meager survival of SACC patients [7]. The available SACC diagnostic includes ultrasound, computed tomography, and magnetic resonance imaging, each with varying sensitivities and specificities [8,9]. In addition, the therapeutics associated with SACC are chemotherapy and radiotherapy treatments [10]. However, these diagnostic procedures and treatments are ineffective due to the lack of proper understanding of the molecular mechanism of SACC [11]. Hence, an effective measure is urgently needed for the timely diagnosis and prognosis of SACC. Moreover, the molecular mechanisms that regulate the invasion and metastasis of SACCs are also essential in developing novel therapeutic methods to save our loved ones.

Interestingly, we and others have shown that non-coding RNAs (ncRNAs) such as miRNAs, long non-coding RNAs, piwi RNAs (PIWI-interacting RNAs), and circular RNAs could be used as reliable biomarkers to detect early stages of cancer and malignant growth in clinical settings [12,13]. We have also shown that these ncRNAs modulate various cancer hallmarks, such as proliferation, growth, metastasis, etc., by regulating multiple cancer signaling pathways and genes [14]. As per the theme of the review herein, we have discussed in detail the role of miRNAs in SACC. miRNAs are small non-coding RNAs composed of approximately 19-23 nucleotides that can either regulate or completely inhibit messenger RNA activity, ultimately leading to mRNA degradation [15]. Also, evidence suggests that miRNAs can aid in early cancer

* Corresponding author.
E-mail address: aklankjain@gmail.com (A. Jain).
[1] These authors equally contributed to this work.

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detection, supported by their aberrant expression in various cancer types and their sub-types [16–18]. Although miRNAs do not code for any protein, their capability remains stable in the extracellular matrix even after their release from a cell. Moreover, miRNAs can easily be quantified using polymerase chain reaction methods, making them a good candidate for diagnostic/prognostic monitoring of cancers [19]. Furthermore, despite standard tissue biopsy, measuring the circulating expression levels of miRNAs could significantly support the detection of the tumors without rendering them invasive [20]. Keeping in view the problem associated with SACC, herein, we systematically researched the

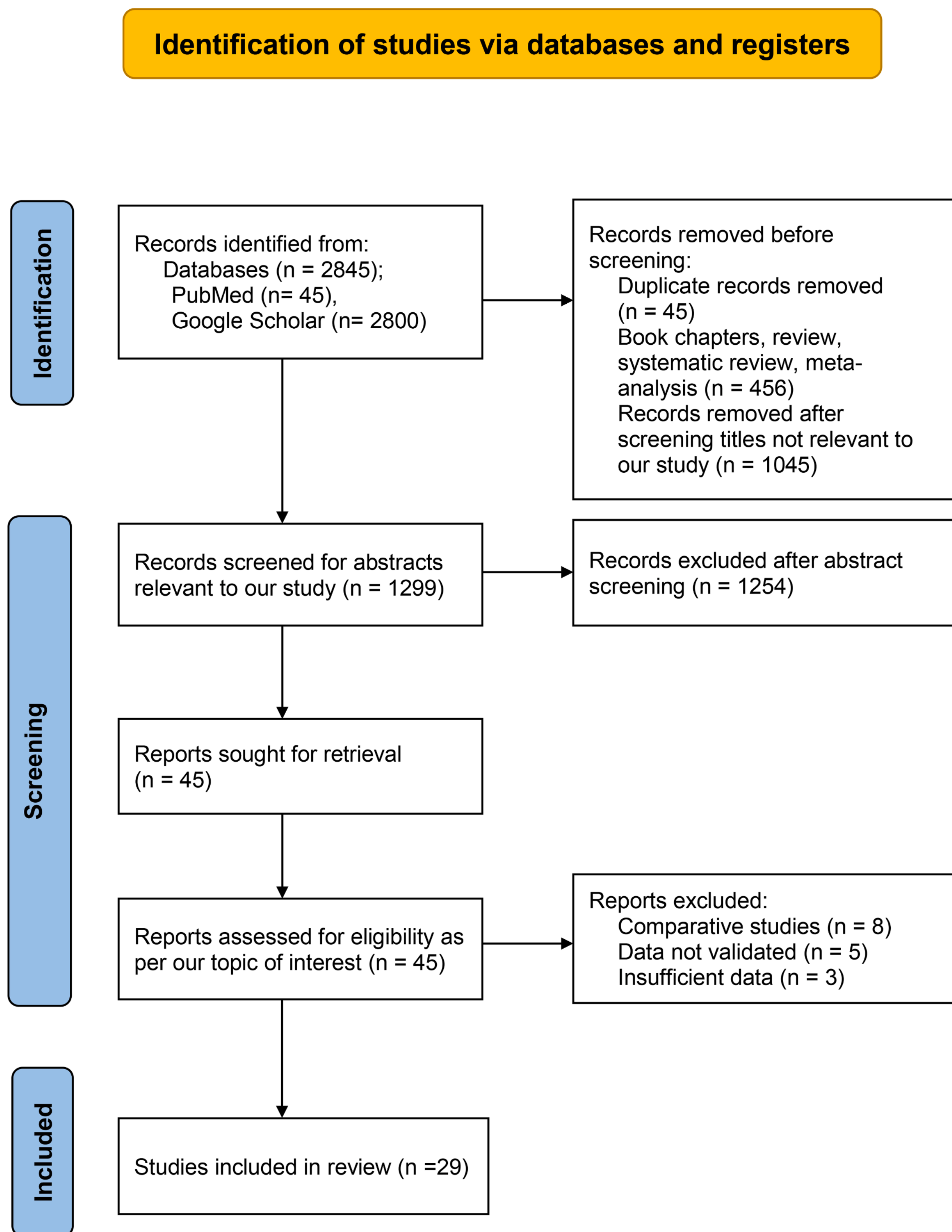

Fig. 1. PRISMA flow chart describing the process of literature search and study selection related to miRNA and salivary adenoid cystic carcinoma (SACC). A total number of twenty-eight relevant studies are incorporated in this review.

role of various miRNAs in the oncogenesis of SACC. Specifically, we have focused on how miRNAs related to SACC affect the diverse cancerous pathways and whether they play as cross-talk molecules. We have also suggested their utility in the diagnosis and prognosis of SACC. The knowledge obtained from this review may help find the molecular mechanisms of the pathogenesis of SACC, specifically the metastasis process, and provide potential markers and targets for the diagnosis and treatments of SACC.

As a summary the current review explains the role of four oncogenic miRNAs (miR-155, miR-21, miR-103a-3p and miR-130a) with miR-155 (fold change= +17.66) being most upregulated miRNA and ten tumor suppressor miRNAs (miR-140-5p, miR-582-5p, miR-101-3p, miR-144-3p, miR-320a, miR181a, miR-98, miR-125a-5p, miR-143-3p, miR-187) with miR-187 (fold change= 8) most downregulated miRNA in SACC progression.

Methodology

PubMed and Google Scholar databases were searched with the keywords [(("Salivary adenoid cystic carcinoma" OR “SACC”) AND ("miRNA"))], and [(("Salivary adenoid cystic carcinoma" OR “SACC”) AND ("microRNA"))]. Studies published between the period 2012-2022 were taken into consideration for our study. We have taken into account only English original articles for further assessments. Next, we screened them based on the study types such as *in-silico, in-vitro* and *in-vivo* studies relevant to our topic. Only those studies were included in which salivary adenoid cystic carcinoma tissue samples and cell lines were studied for aberrant expression of miRNA and reported their clinical correlation with clinicopathological features of the human patients. The duplicate study and insufficient qualitative data were excluded. Studies published in the meta-analysis, reviews, and book chapters were excluded. Finally, twenty-nine original research articles were found relevant to our study. We utilized the standard PRISMA 2020 format of literature search, and the whole process, along with the results, is demonstrated in Fig. 1.

Further, based on the expression levels in SACC tissues compared to normal salivary tissues from the studies, miRNAs can be divided into oncogenic and tumor suppressor miRNAs. Summarized information of these two subsets of miRNA is represented in tabular form (Tables 1 and 2).

Diverse miRNAs affecting SACC progression

According to the perceived studies, some of the many aberrant miRNAs were more readily associated with SACC carcinogenesis. Some act as oncogenic miRNA and other tumor suppressor miRNA. To understand how they play such roles and their significance in SACC diagnostics and therapeutics, we compiled this study to give an overview of various miRNAs associated with SACC pathogenesis. In section **3.1**, we have discussed oncogenic miRNAs, whereas, in section **3.2**, we have discussed tumor suppressor miRNAs related to SACC.

Oncogenic miRNAs in salivary adenoid cystic carcinoma (SACC)

miR-155

miR-155 is usually transcribed from the *B-cell integration cluster (BIC)* gene located at chromosome 21q21.3. It regulates various immune system processes, including inflammation and immune memory in activated myeloid and lymphoid cells [38]. The expression level of miR-155 plays a significant role in tumorigenesis and invasion in various cancers, as shown in Fig. 2. For example, the upregulated overexpression of miR-155 correlates with the progression and development of several cancers such as human T-cell leukemia [39], thyroid carcinoma [40], breast cancer [41], colon cancer [41], cervical cancer [42], pancreatic ductal adenocarcinoma [43], lung cancer [41], B-cell malignancies [44] and Hodgkin’s lymphoma [45]. While most of the research confirmed that miR-155 plays a role in oncogenesis, some studies also suggest its role as a tumor-suppressor in cancer, such as in multiple myeloma [46] and non-small cell lung cancer [47–49].

Concerning SACC, Liu et al. examined the expression level of miR-155 through qRT-PCR in ten SACC patients compared to eight healthy controls [21]. They observed that miR-155 overexpresses in SACC patients compared to healthy controls. Furthermore, the authors also observed similar results in SACC-2 primary tumor cells derived from the SACC patients. Mechanistically, lentivirus-mediated knockdown of miR-155 in SACC-2 primary cells leads to a decrease in cell proliferation and an increase of cells in the G1 phase of the cell cycle. Moreover, knocking down miR-155 significantly suppresses the invasive ability of SA4C-2 cells. Furthermore, knockdown of miR-155 in 4-6 weeks old BALB/C mice leads to slower tumor growth, and even the metastatic tumors were found to be lower in this group of mice compared to the control group. The authors have also evaluated whether any correlation exists between miRNA-155 and epidermal growth factor receptor (EGFR)/NF-κB in SACC cells. It was observed that miR-155 expression is directly correlated with the expression of RelA and epidermal growth factor receptor (EGFR) (Fig. 3) [21]. Previously, several studies have proven the role of the EGFR/NF-κB pathway in the growth and metastasis of many malignant tumors [50]. Overexpression of EGFR causes induction of tumorigenesis and angiogenesis, and metastasis in cancer patients. Moreover, another study conducted by Feng et al. reported that miR-155 is highly expressed in SACC-LM cell lines, and *Ubiquitin-like 1-activating enzyme E1B* (*UBA2)* is found to be the target gene in SACC tissues (Fig. 3 and Table 1) [22].

Table. 1
Oncogenic miRNAs in Salivary adenoid cystic carcinoma.

S. No.	miRNA	Genomic location	Identified functions	Possible Target Genes/ Proteins	Approx. fold change	Number of patient’s samples	Number of controls	Cell lines	Refs.
1.	miR-155	21q21.3	Facilitates cell cycle progression and promotes invasion in SACC by targeting EGFR/ NF-kB pathway	EGFR/ NF-kB, UBA2, Rela (p65)	↑ 17.66	10 tumor cases of ACC	8 cases of normal parotid gland (PG)	ACC-2	[21, 22]
2.	miR-21	17q23.1	Promotes SACC cell proliferation and metastasis, Inhibits SACC cell apoptosis	PDCD-4, Stat3, PTEN, Bcl-2	↑ 6.10	37 cases of resected SACC	20 cases of normal salivary gland tissues (NSGs)	SACC-LM, SACC-83	[23, 24, 25]
3.	miR-103a-3p	5q34	Promotes metastasis by targeting *TPD52* in SACC	TPD52	↑ 2.00	10 human SACC tissues	10 paired healthy submandibular gland (SMG) tissues	SACC-83, SACC-LM	[26]
4.	miR-130a	11q12.1	Promotes SACC cell proliferation and metastasis by targeting NDRG2 proteins	NDRG2	↑ 15.34	21 fresh primary SACC human tissues	21 normal salivary glands (NSG) tissues	SACC-83-NDRG2-sh1/-sh2, SACC-LM-NDRG2-sh1/ sh2	[27]

↑ - Upregulation

Table. 2
Tumor Suppressor miRNAs in Salivary adenoid cystic carcinoma

S. No.	miRNA	Genomic location	Identified functions	Possible target Genes/ Proteins	Approx. Fold-change	Number of patient samples	Number of controls	Cell lines	Refs.
1.	miR-140-5p	16q22.1	Inhibit cell proliferation and invasion and increase cell apoptosis by targeting Survivin	Survivin	↓ 1.17	35 SACC clinical tissues	35 normal salivary gland (NSG) tissues	SACC-83, SACC-LM	[28]
2.	miR-582-5p	5q12.1	Inhibits invasion and migration of SACC cells by targeting *FOXC1*	FOXC1	↓ 2.75	6 primary human SACC samples for microarray analysis, 16 primary human SACC samples for real time-PCR	6 adjacent normal tissues for microarray analysis, 16 adjacent normal tissues for real time-PCR	ACC-2, SACC-83	[29]
3.	miR-101-3p	1p31.3; 9p24.1	Suppresses cell proliferation and invasion and increases chemotherapeutic sensitivity in SACC by targeting *Pim-1*	Pim-1	↓ 1.60	30 SACC tissue samples	10 normal parotid glands	SACC-83, SACC-LM	[30]
4.	miR-144-3p	17q11.2	Inhibits proliferation and induces apoptosis of human SACC cells via targeting of mTOR	mTOR	NA	NA	NA	SACC-83, SACC-LM	[31]
5.	miR-320a	8p21.3	Inhibits metastasis of SACC cells by targeting *ITGB3*	ITGB3	NA	302 SACC patients, 148 SACC patients	U6 was used as an internal control	ACC-M, ACC-2, SACC-LM, SACC-83	[32]
6.	miR-181a	9q33.3	Tumor suppressor, Inhibits metastasis via MAPK- Snai2 pathway	MAPK-Snai2 pathway	↓ 2.50	NA	NA	SACC-83, SACC-LM	[33]
7.	miR-98	Xp11.22	Act as a tumor suppressor and inhibits proliferation and metastasis by targeting *N-RAS*	N-RAS	↓ 2.40	43 fresh tissues from SACC patients	Phosphate buffered saline (PBS) was used as a negative control	ACC-M, SACC-83	[34]
8.	miR-125a-5p	19q13.41	Act as a tumor suppressor and inhibits cell proliferation via targeting p38	P38	NA	106 SACC patient's tissue samples	Paired, adjacent non-neoplastic tissue (ANT) samples of salivary glands were obtained from 20 of these patients	SACC-83, SACC-LM	[35]
9.	miR-143-3p	5q32	Inhibits metastasis by targeting ITGA6 and downstream PI3K/ Akt and MEK/ERK signaling pathway	ITGA6, PI3K/Akt and MEK/ ERK	↓ 1.78	102 SACC tissue samples	Adjacent normal salivary tissues (No. not specified)	SACC-83, SACC-LM	[36]
10.	miR-187	18q12.2	Suppress SACC cell migration, invasion, and PNI ability by targeting CXCR5	CXCR5	↓ 8.00	158 SACC patient's tissue samples	20 cases of normal salivary glands (NSG)	SACC-LM	[37]

NA- Not Available ↓ - Downregulation.

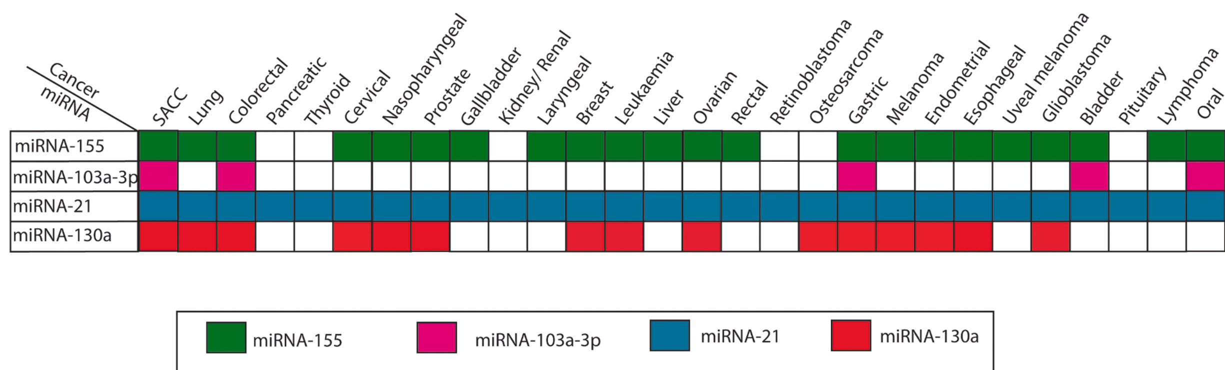

Fig. 2. Oncogenic miRNAs found in SACC also play a role in other human cancers. The shaded squares represent the active role of given miRNA in the cancer mentioned above.

Overall, from the above results, we can speculate that miRNA-155 may be used as diagnostic and prognostic markers for SACC patients, though further detailed work is required. The miR-155/UBA2/EGFR/NF-κB axis may be explored as a new therapeutic target for SACC.

miR-21

The miR-21 is one the best-studied miRNAs among all miRNAs. It primarily works as an oncogenic miRNA (Fig. 2). It regulates different signaling pathways and their related targets, including programmed cell death 4 (PDCD4), RAS/MEK/extracellular signal-regulated kinase [51, 52], HIF-1alpha/VEGF [53], PTEN and TIMP metallopeptidase inhibitor 3 [23,54].

Jiang et al. studied the role of miR-21 in thirty-seven resected tissue samples of SACC patients [24]. They found a higher expression level of miR-21 in SACC samples compared to standard tissue samples; similar results are also found in SACC-LM (high metastatic potential) and

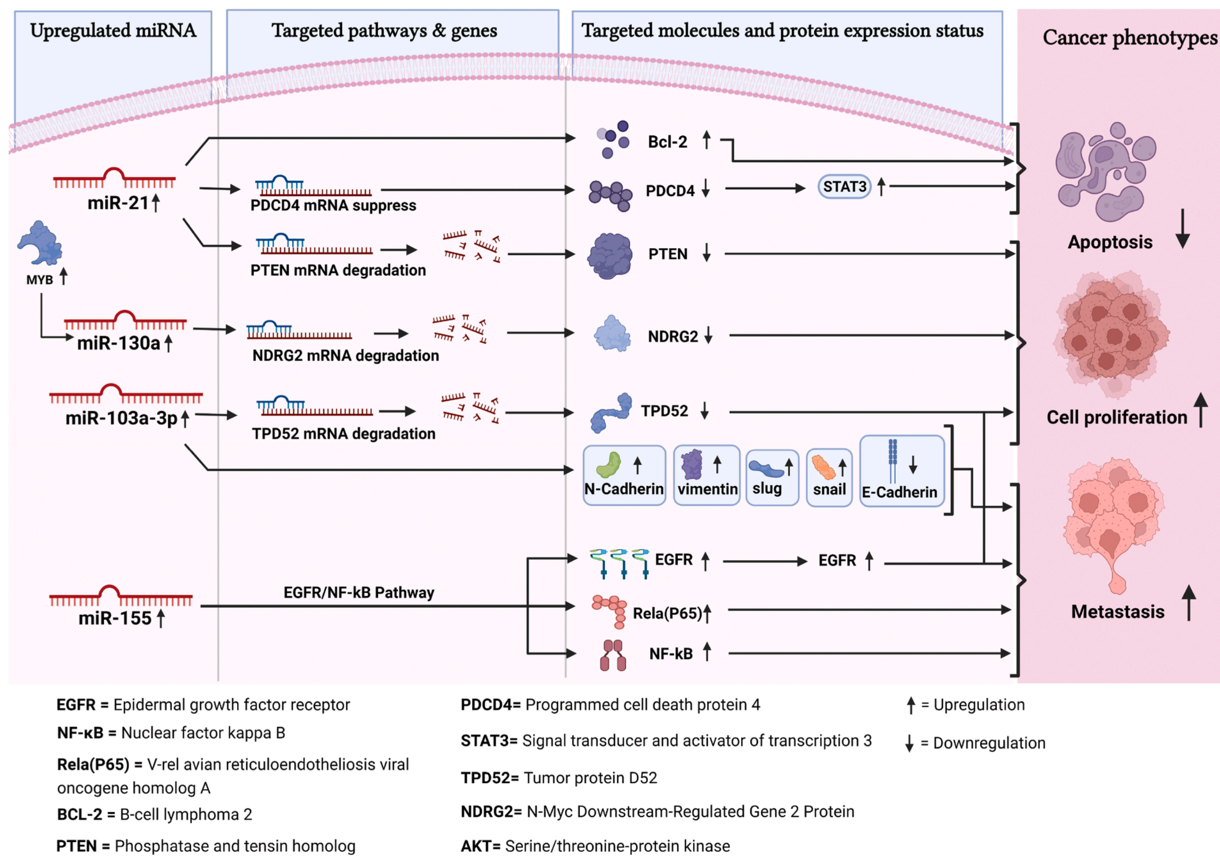

Fig. 3. Role of various miRNAs in salivary adenoid cystic carcinoma carcinogenesis by acting as Oncogenic miRNAs. Overexpressed miR-21 increases Bcl-2 expression while binding and degrading the PDCD4 and PTEN mRNA, which reduces PDCD4 and PTEN levels, lowering Apoptosis and increasing cell proliferation. miR-130a upregulated by transcription factor MYB degrades NDRG2 mRNA, and lower levels of NDRG2 are related to increased cell proliferation. miR-103a-3p degrades TPD52 mRNA and decreases TPD52 levels leading to cell proliferation, while miR-103a-3p increases N-cadherin, vimentin, slug, snail, and decreases E-cadherin, leads to metastasis. Overexpressed miR-155 increases EGFR, related to increased cell proliferation and metastasis, while increased Rela (P65) and NF-kB levels lead to increased metastasis.

SACC-83 (low metastatic potential) cell lines. These results suggest that overexpression (fold change > 5) of miR-21 plays an essential role in the oncogenesis process of SACC [24]. Moreover, higher expressions of miR-21 were also observed in patients of SACC with metastasis compared to patients without metastasis. In addition, Kaplan-Meier analysis indicated that patients with higher levels of miR-21 had a lower disease-free survival rate than those with reduced levels of miR-21. Also, it was found that the overexpression of miR-21 increases the cell's invasive ability compared to the vehicle-transfected cells. On the contrary, the cell invasion rate decreases when the anti-miR-21-based inhibitor is transfected in cells. Likewise, a wound-healing assay showed more migrated cells than negative control cells [24]. These data suggest that miR-21 promotes migration and invasion in SACC tumors. Furthermore, through bioinformatics tools like TargetScan, miRanda, PicTar, and MAMI, PDCD4 was identified as a direct target of miR-21. Next, it was reported that there was a surge in expression levels of protein PDCD4 when the miR-21 inhibitor reduced endogenous miR-21 levels in cells. Signal transducer and activator of transcription 3 (STAT3) was identified as a PDCD4 downstream target since they reported the expression levels of phosphorylated STAT3 protein to be also reduced by miR-21 inhibitor. However, PDCD4 and STAT3 mRNA levels were unaffected by changes in miR-21 levels. Moreover, when endogenous phosphorylated STAT3 expression was knocked down by RNA interference, the expression of PDCD4 protein was considerably raised. Still, the expression of miR-21 levels was reduced, showing that there could be a feedback loop amongst miR-21-PDCD4-p-STAT3 [24]. Besides, immunohistochemistry (IHC) staining revealed that tumor tissues had lower levels of protein PDCD4 and significantly higher levels of protein p-STAT3 than normal salivary gland tissues, as confirmed by western blotting. As a result, they concluded that higher levels of miR-21 in SACC samples are associated with low PDCD4 protein levels and high p-STAT3 levels [24].

Similarly, Yan F et al. also studied the contribution of miR-21 in the growth and metastasis of human SACC. They used two types of cell lines, i.e., SACC-LM and SACC-83. The qRT-PCR results indicate that SACC-LM cells having overexpression of miR-21 showed higher metastatic potential [55]. When SACC-LM cell lines were transfected with miR-21 inhibitors, the viability of the cell was also reduced. This may be due to the onset of apoptosis, lower proliferation, and metastasis measured by CCK-8, wound healing, and matrigel invasion assay. Moreover, bioinformatics databases, including TargetScan, miRanda, and miRbase, were used to determine the potential target genes of miR-21, including *PDCD4* and *B-cell lymphoma-2 (Bcl-2)*, and *PTEN* [55]. In SACC-LM cells, western blotting results showed a negative correlation between miR-21 expression with PTEN and PDCD4 protein expression and a positive correlation with Bcl-2 protein levels [55]. These results suggest that miR-21 can foster SACC progression via PTEN, PDCD4, and Bcl-2 pathways. Furthermore, when SACC-LM cells were transfected with miR-21 siRNA to downregulate the expressions of miR-21, this downregulation prompts adverse effects on the growth of the tumor. It brings positive effects on apoptosis [55]. These transfected cells with miR-21 siRNA exhibit a rise in annexin V staining, which is associated with higher apoptosis, which indicates miR-21 silencing is associated with increased tumor apoptosis. Wound healing assay results suggested that the silencing of miR-21 in SACC-LM reduced migratory properties. Similar results were obtained in matrigel invasion assay as silencing of

miR-21 decreases the population of cells crossing the membrane compared to negative control siRNA transfected group cells [55]. Furthermore, western-blot results of metastasis-associated markers show that Snail protein is downregulated and E-cadherin is upregulated, while GAPDH expression remains constant. All of these findings suggest that miR-21 positively affects the development of invasive and migratory properties in SACC-LM cells. SACC genes such as *PDCD4, PTEN*, and *Bcl-2* play essential roles in migration, invasion, and apoptosis and are potential targets of miR-21. When miR-21 is silenced with siRNA, it increases PTEN and PDCD4 mRNA levels while decreasing Bcl-2. As a result, these findings suggest that miR-21 may promote metastasis and tumor cell proliferation while reducing cell apoptosis by regulating its various target genes PDCD4, PTEN, and Bcl-2 [55]. Afterward, Wang et al. studied simvastatin (SIM) with the combination of miR-21 inhibitors and found that their combination significantly inhibits SACC-LM migration, invasion, and cell viability while increasing apoptosis [25]. Moreover, western blot results demonstrated that E-cadherin expression was upregulated and snail1 expression was downregulated in SIM, miR-21 inhibitor-treated cells indicating the role of the epithelial-mesenchymal transition (EMT) pathway. Again, western blot analysis was performed, whose results demonstrated that SIM and miR-21 inhibitors induce apoptosis by inhibiting Bcl-2 protein expression while increasing P53 and Bax protein levels [25]. Finally, they concluded that SIM and miR-21 inhibitors control Bcl-2, P53, Bax, and G0/G1 phase-related proteins such as CDK2, CDK4, and CDK6 to increase apoptosis, as shown in Fig. 3 and Table 1. So, the miR-21 inhibitor could be favorable for reducing SACC-LM SIM resistance.

Finally, we concluded that miR-21′s vital role in developing SACC and that miR-21 target-based therapy medicines can be used to treat SACC. Also, miR-21 could be a possible diagnostic biomarker in SACC patients.

miR-103a-3p

miR-103a-3p is 23 nucleotide miRNA located on chromosome-5. It shows double edge sword properties in cancers. For example, it elevates the oncogenesis in cervical cancer [56], liver [57], gastric cancers (GC), and SACC [58], whereas decreasing the chances of glioma [59] and non-small cell lung cancer (NSCLC) [60] (Fig. 2). In addition, many target molecules associated with miR-103a-3p, such as NF-κB/p65, YAP1, and PDCD4, are involved in the cancer progression [61,62].

Fu et al. studied the oncogenic role of miR-103a-3p in the SACC [26]. The authors found that miR-103a-3p overexpresses in SACC tissues ($n = 52$) compared to SMG tissues ($n = 38$) [26]. They also observed significant upregulation of miR-103a-3p in SACC-LM, SACC-83 cell lines, and SACC cell exosomes. Although, no significant correlation was found between miR-103a-3p expression and clinicopathological characteristics like the clinical stage, tumor size, site, perineural invasion, and pathological type [26]. At the same time, the local recurrence and lung metastasis were associated with miR-103a-3p overexpression. To further explore its role in various biological processes, CCK8 wound healing and transwell assay was performed, demonstrating that miR-103a-3p had no significant role in SACC cell proliferation. But miR-103a-3p regulates a significant role in SACC cell migration and invasion as the level of EMT-related protein markers such as N-cadherin, vimentin, slug, and snail increases, while epithelial markers like E-cadherin decrease [26]. An *in-vivo* study performed on NOD/SCID mice also gave similar results as mice injected with miR-103a-3p mimic transfected SACC-83 cells had a significantly higher number and extent of clearly visible lung tumor nodules compared to the negative control mice [26]. Next, bioinformatics tools like TargetScan, miRbase, and miRDB were used to investigate the potential interaction of miR-103a-3p with its target mRNAs, and they identified *tumor protein D52* (*TPD52)* as a target of miR-103a-3p [26].

The luciferase reporter assay and qRT-PCR and western blotting results indicated TPD52 as the direct target of miR-103a-3p negatively correlated, as demonstrated in Fig. 3 and Table 1. In addition, the expression levels of TPD52 were also analyzed in 38 SMG and 52 SACC samples [26]. Results were in accord with previous findings as higher expression of TPD52 in healthy tissues was found compared to SACC tissues. These findings suggest that miR-103a-3p promotes metastasis by directly targeting the *TPD52*.

Thus, miR-103a-3p overexpression is linked to local recurrence and lung metastasis. Furthermore, it also regulates EMT-related protein markers, which play a crucial role in SACC cell invasion and migration, making the SACC even worse. Additionally, it was reported that in contrast to the negative control, in an *in-vivo* experiment, transfected cells had a much greater number and size of plainly visible lung tumor nodules. Thus, miR-103a-3p could be a prognostic marker in SACC patients.

miR-130a

miR-130a is a precursor miRNA located at chromosome 11. It plays a dual role in different types of cancers (Fig. 2); for example, in the prostate [63] and glioma cancer [64], it acts as a tumor suppressor, whereas in GC [65], NSCLC [66], and colorectal cancer (CRC) [67] serves as an oncogene. Previous studies have demonstrated the role of miR-130a in inhibiting autophagy by downregulation of *ATG2B* and *DICER1* genes in chronic lymphocytic leukemia (CLL) [68] and gastrointestinal stromal tumors (GISTs) [69].

Wang et al. studied the role of the MYB/miR-130a/*NDRG2* axis in the progression and metastasis of SACC. Primarily they focused on the expression of N-downstream-regulated gene 2 (*NDRG2)* in SACC tissue samples [27]. *NDRG2* is a pleiotropic tumor suppressor gene having roles in various biological processes such as apoptosis, reprogramming of cellular metabolism, senescence, and cell cycle arrest [70,71]. Their study found that *NDRG2* is a downstream target of miR-130a, having the target sequence present over 3'-UTR of its mRNA and playing a role in SACC progression. The results of qRT-PCR showed downregulated *NDRG2* expression, which has a significant association with poor overall survival and high distant metastasis [27]. To explore the role of *NDRG2* in biological processes in SACC, the authors used shRNA-transfected SACC-83 and SACC-LM cells and performed a CCK8 and colony formation assay. Results of these assays confirmed that low expression of *NDRG2* promotes cell growth in both cell lines and has a high tumorigenic potential [27]. Afterward, wound healing and transwell assay was performed to ensure the role of NDRG2 in distant metastasis and invasion. The above showed that downregulation of *NDRG2* enhanced SACC cell migration and invasion significantly [27].

Furthermore, an *in-vivo* study in a xenograft tumor mouse model with *NDRG2* silencing showed huge tumor size and increased tumor weight. Moreover, mice infected with *NDRG2* knockdown SACC-LM cells developed massive metastatic nodules and high importance of lungs with metastasis [27]. A western blot analysis was performed to confirm that NDRG2 is the downstream target of miR-130a. The results indicate that miR-130a inhibition upregulates NDRG2 protein expression, whereas miR-130a mimics downregulates NDRG2 protein expression in a dose-dependent manner in SACC-83 and SACC-LM cell Fields (59). This was further validated by using a dual-luciferase reporter assay. miR-130a acts as an oncogene, as demonstrated by qRT-PCR results in 76.2% of SACC tissues. To explore the mechanism of the miR-130a and its downstream pathway in SACC. Researchers created SACC cell lines with miR-130a overexpression using lentiviral vectors and found that NDRG2 mRNA and protein levels declined compared to control cells [27]. CCK8, colony formation, wound healing, and transwell assays illustrated that miR-130a overexpression promotes cell proliferation, migration, and invasive capacity of the SACC cell line. Consistent with the above *in-vivo* study also revealed that miR-130a overexpression enhanced tumor progression, metastatic ability to lungs, and several nodules in the mouse lungs [27]. Ectopic NDRG2 protein levels inhibit cell growth, colony formation, and invasion caused by miR-130a in SACC-83 and SACC-LM cell lines [27].

Many studies have demonstrated that miR-130a could be activated

through transcription factors such as SOX9 and NF-κB. MYB is one of the transcription factors that is known to be a master oncogenic driver in SACC. So, by using the MYB knockdown strategy and western blot, they found that decreased MYB significantly increased the NDRG2 expression, whereas miR-130a gets downregulated in SACC cell lines [27]. They searched databases such as miRStart and JASPAR to find any canonical sequence of MYB in the miR-130a promoter region, and the results display six MYB binding sites. After confirmation of the CHIP qPCR assay, they concluded that MYB act as a transcription factor upregulating miR-130a expression by binding at five promoter binding sites [27]. Furthermore, to uncover any downstream target after *NDRG2* in MYB/miR-130a/*NDRG2* axis, they used a knockdown strategy, and results indicate that downregulated *NDRG2* expression and MYB/miR-130a overexpression induced the protein level of pSTAT3 and pAKT and vice-versa as illustrated in Fig. 3 and Table 1 [27].

From the above data, we conclude that overexpressed MYB being an upstream transcription factor upregulates miR-130a, which further inhibits *NDRG2*, a critical tumor suppressor gene leading to SACC progression via STAT3 and AKT pathways. Thus, miR-130a could be considered a diagnostic biomarker, whereas NDRG2, its downstream molecule, could act as a therapeutic target.

Tumor Suppressive miRNAs in salivary adenoid cystic carcinoma (SACC)

miR-140-5p

miR-140-5p is a 22-nucleotide long miRNA located on chromosome 16q22.1 and works as a tumor suppressor, as illustrated in (Fig. 4). It was revealed that miR-140-5p inhibits tumor invasion and angiogenesis by targeting vascular endothelial growth factor A (VEGF-A) in breast and larynx carcinoma [72,73]. In addition, targeting fibroblast growth factor 9 (FGF9) modulates the bladder cancer phenotype and cell aggressiveness [74]. In the case of GC, miR-140-5p directly binds with the Yamaguchi sarcoma viral oncogene homolog 1 (YES1), and member of the Src family tyrosine kinase, and inhibits invasion, cell proliferation, and migration [75].

Qiao et al. studied 35 samples of SACC patients who underwent surgery along with two SACC cell lines, i.e. (SACC-83 and SACC-LM). They reported that upregulation of miR-140-5p leads to inhibition of SACC cell proliferation, invasion, growth of the tumor, and increased cell apoptosis [28]. On the other hand, downregulation of miR-140-5p has opposite effects on tumor-like enhancement in invasion, proliferation, tumor growth, and decreased apoptosis. miR-140-5p targets 3'-UTRs of surviving and regulates the effects of survivin inversely (66). Survivin is a member of the inhibitor of apoptosis protein (IAP) family, inhibits the expressions of caspases, and prevents programmed cell death. The knockdown of survivin has tumor-suppressive effects on SACC cells, and the increased expression of survivin acts against the tumor-suppressive effects of miR-140-5p [28]. In colony formation assay, it was found that the higher expression of miR-140-5p reduces the total number of colonies growing compared with the negative control groups. In the CCK-8 assay, the miR-140-5p overexpression reduced cell proliferation in SACC-83 and SACC-LM [28]. In the transwell invasion assay, SACC-83 and SACC-LM were transfected with miR-140-5p mimics and its negative control, and results showed a reduction in invasive cell number compared with negative control groups.

Further, higher expression of miR-140-5p in SACC-83 and SACC-LM enhances caspases-3 activity, which induces apoptosis [28]. Luciferase activity assay showed that overexpression of miR-140-5p targets 3'-UTR of survivin and suppresses the luciferase activity Luc-survivin 3'-UTR-WT when compared with NC mimics group. Still, the luciferase activity of Luc-survivin 3′UTR-MUT was not affected by the overexpression of miR-140-5p [28]. The qRT-PCR and western blot assays showed that the higher expression of miR-140-5p suppresses the survivin mRNA and protein expression levels in both cell lines. At the same time, the knockdown of miR-140-5p upregulates the survivin expression [28]. So, we can say that survivin is the potential target of miR-140-5p. These results were further tested by using YM-155 (survivin suppressant), which suppressed the cell proliferation, growth, and invasion in SACC-83 and SACC-LM cell lines. In addition, YM-155 treatment also increases cell apoptosis rates and caspases-3 activity of SACC-83 and SACC-LM [28]. Further, (Fig. 5 and Table 2) depict how levels of cleaved caspase-3 and caspase-9 are enhanced by higher expression of miR-140-5p and how this overexpression is reducing the levels of XIAP protein. miR-140-5p overexpression reduces the expression of N-cadherin, vimentin, MMP-2, and MMP-9 and increases the expression of E-cadherin [28].

In conclusion, miR-140-5p can be a potential biomarker and therapeutic target. Downregulation of miR-140-5p has been confirmed in

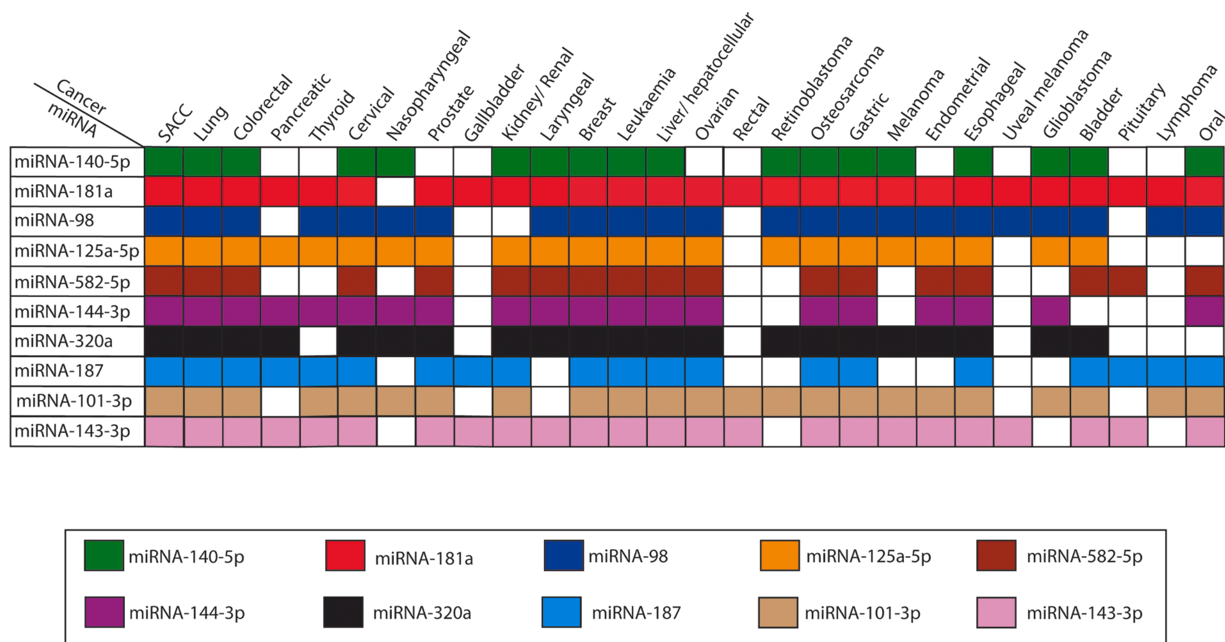

Fig. 4. Tumor suppressor miRNAs found in SACC also play a role in other human cancers. The shaded squares represent the active role of the given miRNA in cancer mentioned above.

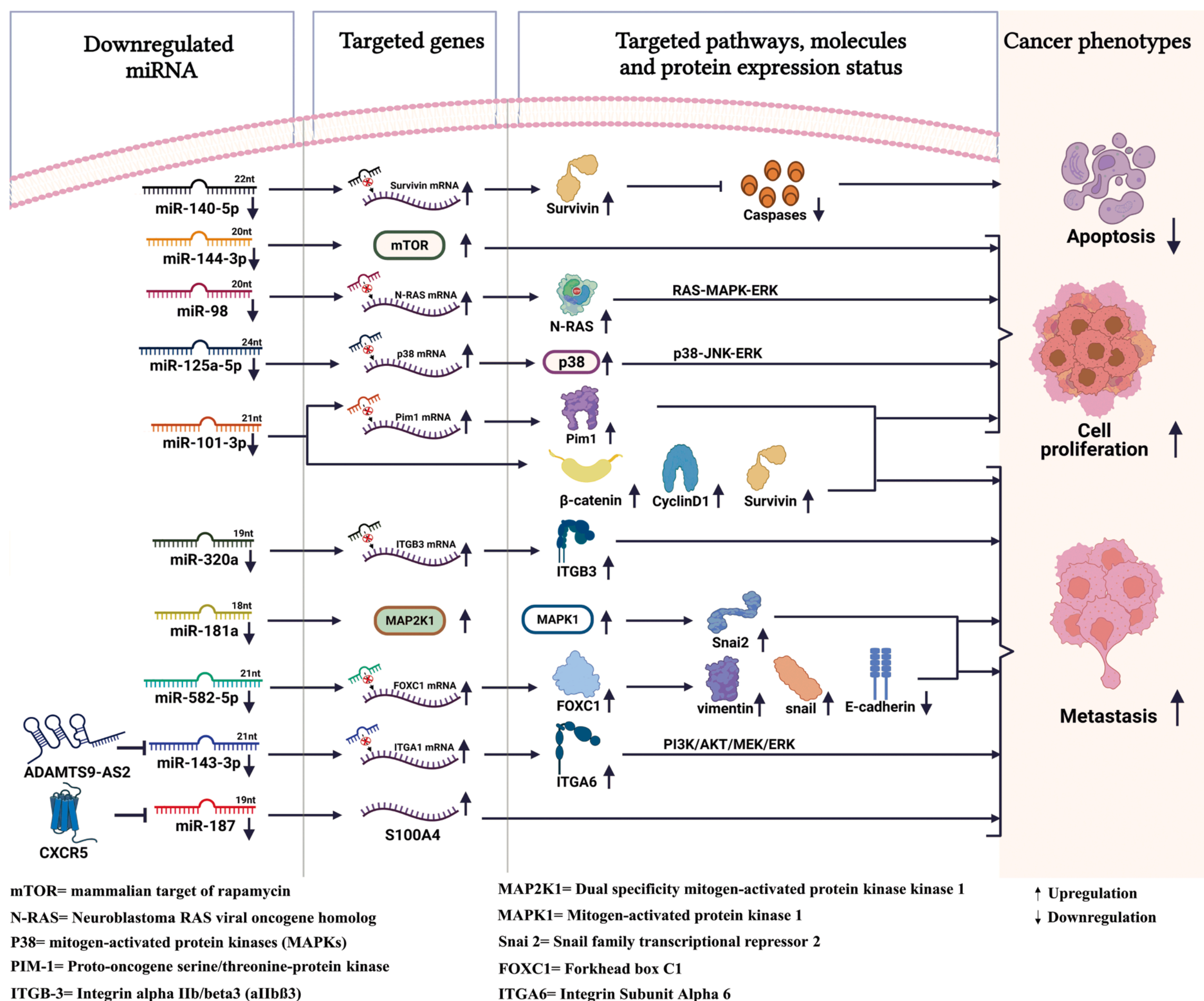

Fig. 5. Role of various miRNAs acting as tumor suppressor miRNAs in salivary adenoid cystic carcinoma carcinogenesis The downregulation of miR-140-5p, miR-144-3p, miR-98, miR-125a-5p, miR-101-3p, miR-320a, miR-181a, miR-582-5p, miR-143-3p, and miR-187 make them unable to degrade mRNA of survivin, mTOR, N-RAS, p38, Pim1, ITGB3, MAP2K1 FOXC1, ITGA1 and S100A4 respectively which further upregulate their protein level. This increased expression of N-RAS, p38, Pim1, B-catenin, and cyclin-D1 proteins further contributes to cell proliferation. In contrast, an increased level of survivin protein suppresses the caspase level resulting in inhibition of the cell apoptosis. In addition, increased expression of ITGB3, FOXC1, ITGA1, and S100A4 results in increased metastasis.

SACC, and its higher expression inhibits SACC progression primarily via targeting survivin protein.

miR-582-5p

miR-582-5p is located on chromosome 5 and plays a crucial [76] tumor suppressor in many human cancers (Fig. 3). In hepatocellular carcinoma (HCC), miR-582-5p performs tumor-suppressive effects by inhibiting the expression of cyclin-dependent kinase1 (CDK1) [77]. In human colorectal carcinoma, miR-582-5p performs tumor-suppressive effects by targeting the gene Rab27a [78].

Wang et al. have taken two SACC cell lines which are ACC2 and SACC-83. They performed miRNA microarray analysis and qRT-PCR and found that miR-582-5p was the most downregulated miRNA among various miRNAs in SACC compared to normal tissues [29]. They compared the expression of SACC-83 and ACC2 with the human salivary gland (HSG) cell line derived from cells of salivary glands expressing non-neoplastic lesions. They reported that the expression levels of miR-582-5p in SACC-83 and ACC2 were much lower as HSG cell line [29]. This downregulation of miR-582-5p is associated with the initiation of invasion and migration in SACC cells. It was confirmed by Modified Boyden chamber assays, which indicated that miR-582-5p mimics reduced the invasion and migration of SACC-83 and ACC2 cells as compared to control groups, and upregulation of miR-582-5p expression results in lower proliferation of SACC cells as shown by MTT assay meanwhile, it does not show any effects on apoptosis [29]. In brief, these findings demonstrate that upregulating miR-582-5p suppresses the SACC cell invasive and migratory abilities as migration and invasive abilities in SACC-83 cells are reduced by 2.1-2.6 folds and 2.7-3.2 folds in ACC2 cells. Still, it promotes cell proliferation *in-vitro* [29]. Next, they used TargetScan to anticipate the target genes of miR-582-5p, and their results suggest that miR-582-5p shows complementarity with 3'-UTRs of FOXC1 in SACC cells. After that, the luciferase activity assay indicated that Forkhead Box C1 (FOXC1) expression is inversely associated with miR-582-5p expression (70). Downregulation of FOXC1 expressions reduces the proliferation of SACC cells but does not affect cell apoptosis. FOXC1 downregulation causes a surge in E-cadherin and a decrease in vimentin and snail protein expressions, indicating that FOXC1 may control the EMT of SACC cells by transactivation of the snail [29]. Modified Boyden chamber assays indicate that FOXC1 siRNA and miR-582-5p mimics inhibit migration and invasion in SACC-83 cells compared with control cells. Afterward, they performed IHC and *in-situ* hybridization to know the clinical role of miR-582-5p [29]. So, they compared SACC tissues with normal adjacent tissues and found a strong correlation between FOXC1 and miR-582-5p because, in primary SACC cells, miR-582-5p expression levels were lower and FOXC1 expression levels were higher [29]. As a clinical

significance, lower expression of miR-582-5p was related to the poor prognosis but did not have any link with the age and sex of SACC patients [29].

Interestingly, the results from Kaplan-Meier survival curves indicate that the patients with higher expression of miR-582-5p live longer life than those with lower miR-582-5p indications. Additionally, patients with lower FOXC1 survived longer than those with higher FOXC1 expression [29]. Hence, miR-582-5p is associated with the migration and invasion abilities in SACC via targeting FOXC1. Overexpression of miR-582-5p suppresses invasion and migration in SACC. This study also indicates that in SACC patients, miR-582-5p can act as a prognostic factor of metastasis [29]. In the case of SACC, the expression of miR-582-5p was downregulated, and its target gene FOXC1 was upregulated, as represented in (Fig. 5 and Table 2). So, higher expressions of miR-582-5p can suppress invasion and metastasis [29].

In conclusion, the above findings suggest that miR-582-5p can act as a tumor biomarker in SACC and may have the potential of being an effective target in therapy, for which it needs further research.

miR-101-3p

miR-101-3p plays a role of a tumor suppressor as it has been significantly downregulated in numerous types of cancers (Fig. 4), including prostate [79], breast [80], glioma [81], HCC [82,83], and osteosarcoma [84]. miR-101-3p is 21 nucleotides long, and its sequence is found in the genome location on Chr.1p31.3. miR-101-3p inhibits HCC progression and metastasis by repressing enhancer of zeste homolog 2 (EZH2) protein expression [85]. Studies also revealed that miR-101-3p inhibits breast cancer cell proliferation and promotes apoptosis [80].

Liu et al. investigated the expression of miR-101-3p using qRT-PCR in thirty SACC tissue samples which were remarkably reduced in contrast with the often-normal parotid glands tissue samples. The results confirm the role of miR-101-3p as a tumor suppressor in the SACC [30]. Two SACC cell lines, SACC-LM and SACC-83, were studied to check miR-101-3p expression. SACC-LM being more malignant has a higher expression of miR-101-3p than the SACC-83 cell line. Downregulation of miR-101-3p is associated with invasion and migration in SACC cells, as confirmed by the matrigel invasion assay [30]. Both cell lines expressing miR-101-3p demonstrated increased apoptosis rates in flow cytometry results.

Moreover, the MTT cell proliferation assay confirmed the role of miR-101-3p as a cell proliferation inhibitor in SACC-83 and SACC-LM cells [30]. The *in-vivo* study also revealed that overexpressed miR-101-3p significantly subjugated the tumor growth resulting in higher tumor weight than the vector group. To unravel the molecular targets of miR-101-3p, western blot analysis of proteins lysed from xenograft tumor was done and interpreted that it downregulates Pim-1, survivin, cyclin D1, and β-catenin [30]. The bioinformatics tools show that Pim-1, a proto-oncogene involved in cancer cell proliferation, migration, and invasion, is the potential target of miR-101-3p [86]. Spearman's rank correlation coefficient and linear tendency tests confirmed that Pim-1 is negatively correlated with miR-101-3p in SACC specimens. Pim-1 is a direct functional target of miR-101-3p, confirmed by luciferase reporter assay and functional restoration assay [30]. Pim-1 and miR-101-3p were also hypothesized to be involved in SACC drug resistance. Further, increased apoptosis rates in SACC cells stably expressing miR-101-3p after 24 h of treatment with cisplatin indicates that miR-101-3p escalates the drug sensitivity of cisplatin in cisplatin in SACC cells [30].

Finally, we can conclude from the above findings that miR-101-3p acts as a tumor suppressor in SACC patients. As per its antitumor mechanism, it downregulates Pim-1, survivin, cyclin D1, and β-catenin proteins involved in cell proliferation, metastasis, and invasion, as shown in (Fig. 5 and Table 2) [30]. Moreover, it also helps boost cisplatin sensitivity in SACC cells. Thus, it could be considered a potential diagnostic and therapeutic target for human SACC.

miR-144-3p

miR-144-3p is a tumor suppressor miRNA located on chromosome 17q11.2, and its downregulation can be seen in different types of cancers (Fig. 4), including NSCLC [87] and liver cancer [88], prostate cancer [89], and GC [90]. In prostate cancer, miR-144-3p is a tumor suppressor by suppressing Centrosomal Protein 55 (CEP55) expressions [89]. In GC, it inhibits tumor progression via targeting Pre-B-cell leukemia transcription factor 3 (PBX3) [90].

Huo et al. studied the roles of miR-144-3p in human SACC cell lines, SACC-83, and SACC-LM concerning tumor proliferation and cell apoptosis via targeting mammalian target of rapamycin (mTOR) [31]. They have used a cell viability assay to evaluate the results of miR-144-3p on SACC cells proliferation.miR-144-3p agomiR (a chemically modified ds miRNA mimic, when transfected into cells, can mimic mature endogenous miRNAs) is used to increase the expressions of miR-144-3p. Transfection of miR-144-3p agomiR into SACC-83 and SACC-LM exhibited the increased expressions of miR-144-3p by 1800-fold in SACC-83 and 1900- fold in SACC-LM cell lines as compared with mock control and other results confirmed that overexpression of miR-144-3p by miR-144-3p agomiR significantly decreases cell proliferation and could inhibit cell survival [31]. Next, the proportion of apoptotic cells transfected with miR-144-3p or mock control was analyzed by flow cytometry, and it was found that 27% of SACC-83 and 37% of SACC-LM were apoptotic. Under fluorescence microscopy, similar patterns were observed in both cell groups using the DAPI staining assay [86]. Here, results indicated that apoptosis is higher in miR-144-3p groups than in mock or scramble control. Afterward, a western blot assay was used to determine the expressions of apoptosis-related proteins in miR-144-3p treated SACC-LM cells. The results indicated that expressions of cleaved-poly-ADP-ribose polymerases (C-PARP) were higher than mock or scrambled control and Bcl-2 expression was lower [31].

Furthermore, they used two bioinformatics database tools, TargetScan and miRanda, to check whether the miR-144-3p expression affects the regulation of proliferation and apoptosis in SACC cells via targeting mTOR. miR-144-3p effect on the mTOR/STAT3 signaling pathway was identified by western blotting. After that miR-144-3p transfection, results indicated lower levels of phospho-S6 (Serine 235/236) (an mTOR downstream molecule) and $pSTAT3^{T3705}$ as compared with mock and scramble controls. In SACC-LM cells, immunofluorescence demonstrated that miR-144-3p reduced p-STAT3 nuclear expression and mTOR cytoplasmic expression [31]. As a result, miR-144-3p targeted mTOR and suppressed its expression in SACCs. Next, they constructed WT and MUT luciferase reporter assay, and their results confirmed that miR-144-3p binds directly to the 3'-UTR of the mTOR mRNA [31]. Moreover, to measure the effects of miR-144-3p agomiR *in-vivo*, a xenograft mouse model was used, and results indicated that after treatment of miR-144-3p agomiR, there was a reduction in tumor growth as compared to scramble control. Then, western blot assay results also confirmed the decreased expression of mTOR, p- mTOR, and Bcl-2 in those tumors treated with miR-144-3p agomiR, as visualized in (Fig. 5 and Table 2) [31].

In conclusion, we can say that miR-144-3p acts as a tumor suppressor in SACC by inhibiting tumor cell proliferation via targeting the mTOR signaling pathway. In SACC-cell lines, overexpressed miR-144 reduced mTOR protein expression. In the progression of SACC, there is downregulation of miR-144-3p expression. Thus, miR-144-3p can be used as a potential biomarker, and miR-144-3p-based therapy can reduce tumor proliferation and can be used to treat SACC patients.

miR-320a

miR-320a expression has been identified in a diverse variety of human tumors, including HCC [91], pancreatic cancer [92], NSCLC [18], breast cancer [93], and CRC [94]. miR-320a present at chromosomal location 8p21.3 [18]. In some tumors, miR-320a serves as a tumor suppressor (Fig. 4), whereas in others, it acts as an oncogene. Zhao et al.

demonstrated that miR-320a plays a tumor-suppressive role by targeting *Rac1* in CRC [94]. Lv et al. revealed that miR-320a is involved in the invasion and metastasis by targeting *HMGB1* and has an anti-metastasis effect in HCC [91].

Previous research indicates that miR-320a expression has almost no effect on SACC cell proliferation or apoptosis. Thus, Sun et al. studied miR-320a expression in metastatic salivary gland cell line ACCM and the parental ACC2 cell line. Microarray and qRT-PCR results demonstrated that miR-320a is significantly downregulated in ACCM cells [32]. miR-320a transfection in SACC-LM and ACCM cells significantly inhibited their adhesion, invasion, and migration as found in transwell assay, and miR-320a silencing produced inverse results confirming that miR-320a acts as a tumor suppressor and its downregulation results in invasion and migration in SACC cells [32]. As per the target genes of miR-320a, a web server named TargetScan estimated *Integrin beta-3 (ITGB3)* to have a recognition site at 3'-UTR. From Luciferase reporter assay and western blot analysis, it was confirmed that miR-320a suppressed ITGB3 expression. miR-320a inhibits the invasiveness of SACC cells by downregulating ITGB3 expression, as demonstrated by rescue experiments [32]. An *in-vivo* study on BALB/c-nu mice inoculated with ACCM cells indicated that miR-320a expression does not affect tumor growth.

Further, Hematoxylin and eosin (HE) staining of the xenografts illustrated that overexpressed miR-320a significantly inhibits ACCM metastasis. Moreover, miR-320a upregulation downregulates ITGB3 expression by more than 60% *in-vivo* but does not affect the number of proliferating PCNA+ tumor cells [32]. Hence, miR-320a inhibits SACC invasion and metastasis via ITGB3 silencing. As per the clinical significance, low miR-320a expression is correlated with poor survival and high metastasis in SACC patients. At the same time, ITGB3 expression was positively associated with distant metastasis in SACC patients [32]. Furthermore, no notable correlation was found between the expression level of miR-320a and sex, age, tumor size, or TNM stage of SACC patients. The multivariate cox regression model demonstrated that miR-320a expression is associated with low lung metastasis in SACC patients; thus, it can be used as an independent biomarker for lung metastasis in SACC patients [32].

Thus, we conclude that miR-320a, a versatile miRNA, plays the tumor suppressor role in SACC. It is mainly associated with the invasion and metastasis of SACC cells with no significant effect on their proliferation and apoptosis. It produces its antitumor effects by silencing ITGB3 expression, as illustrated in Fig. 5 and Table 2. Finally, miR-320a could be considered a prognostic, metastatic biomarker, and therapeutic target in SACC.

miR-181a

miR-181a is a non-coding RNA located on chromosome 1q32.1 [95]. miR-181a plays a role of either a tumor suppressor (Fig. 4) or oncogene depending on the type of cancer. In NSCLC [96], glioma [97], and laryngeal carcinoma [98], miR181a acts as a tumor suppressor. In contrast, in osteosarcoma [99], CRC [100], and acute myeloid leukemia [101], it plays the role of an oncogene. However, in GC, it has a dual role, tumor-suppressive [102] and oncogenic [103]. It has been well established that miR-181a regulates cellular differentiation [104] and also cell proliferation, invasion, and migration in lung cancer [105], papillary thyroid cancer [106], and ovarian cancer [107].

Some studies have already found miR-181a as differentially expressed miRNA in SACC cell lines and tissue samples. He et al. studied miR-181a expression in highly metastatic cell line SACC-LM, and qRT-PCR results confirmed its downregulation [33]. Additionally, they performed scratch assay and transwell assay to further explore the role of miR-181a in SACC. The results show that the expression of miR-181a is inversely correlated with cell proliferation, migration, and invasion [33]. For confirmation, *in-vivo* studies were also done in nude mice, inoculated with SACC-LM cells transfected with miR-181a mimic; interpretation of the tumor growth curve shows increased miR-181a expression significantly inhibited tumor growth and also reduced lung metastasis *in-vivo* [33]. Previous studies have revealed several growth factors (NGF, VEGF, and TGFβ2) and pathways such as MAP-Kinase being involved in SACC proliferation and metastasized [108–110]. To uncover the downstream molecular pathways and target genes, they also investigated the expression levels of VEGF, NGF, TGFβ2, MAPK1, phospho-MAP2K1, and Snai2 in SACC-LM and SACC-83 cell lines after and before transfection with miR-181a mimics [33]. Results of their experiments confirmed that miR-181a shows its antitumor effect by suppressing growth factors and the MAPK-Snai2 pathway. However, VEGF, NGF, and TGFβ2 mRNA were devoid of any miR-181a target sequence [33]. Hence, miR-181a indirectly regulates VEGF, NGF, and TGFβ2 by targeting other factors still to be discovered. Bioinformatic analysis showed the potential target genes from the MAPK pathway: *MAP2K1* and *MAPK1*. Both MAP2K1 and MAPK1 mRNA were reported with target sequences for miR-181a in their 3'-UTR [33]. From the results of dual-luciferase reporter assays using miR-181a mimics and knockdown of MAP2K1 and MAPK1 in SACC-LM cells, it can be identified that MIR-181a suppresses cell migration and invasion by silencing MAP2K1 and MAPK1(103). After confirming the role of the MAPK pathway, they assessed the effect of miR-181a and its targets on *Snai2* gene expression. Previous studies have already established Snai2 as the downstream target of the MAPK pathway in many cancers [111]. Their results also revealed that in SACC, Snai2 acts as a downstream molecule of the MAPK pathway.

Furthermore, Snai2 mRNA was also found to have a miR-181a target sequence suggesting it to be a direct target. Dual-luciferase reporter assay confirmed that miR-181a directly targets Snai2 mRNA as increased miR-181a downregulated Snai2 expression, which ultimately decreased cell migration and invasion in SACC-LM [33]. Thus, miR-181a can either regulate Snai2 expression as a direct downstream target or an indirect downstream target with MAP2K1 and MAPK1 as direct targets, which can be seen in Fig. 5 and Table 2.

Finally, we conclude that miR-181a, another differentially expressed miRNA in SACC cells, acts as a tumor suppressor and is correlated with reduced SACC cell proliferation, migration, and invasion. Thus, miR-181a, with its antitumor effects, can be used as a therapeutic target and be considered a potential diagnostic biomarker.

miR-98

miR-98 is a member of the let-7 family of miRNAs located at chromosome Xp11.22. It works as a tumor suppressor in different types of cancers, as demonstrated in Fig. 4. In colon cancer, it may inhibit the proliferation and invasion of tumor cells via targeting the gene *IGF1R* [112]. In GC, it inhibits cell stemness and chemoresistance via targeting *BCAT1* [113]. In HCC, it inhibits cell proliferation, invasion, migration, and EMT by targeting *SALL4* [114].

Liu et al. studied the role of miR-98 in human SACC tissues (43 tissue samples) and cell lines ACC-M and SACC-83. Online bioinformatics databases such as TargetScan, miRanda, and PicTar were used to recognize the possible target genes of miR-98 [34], and *N-RAS* was found as a potential target gene of miR-98. The *N-RAS* gene is a member of the RAS family, which regulates cell proliferation and metastasis. The qRT-PCR results indicate lower expression of miR-98 in ACC-M cells than in SACC-83 cells [34]. In tumor tissues and ACC-M cells, the miR-98 expressions were lower as compared to adjacent controls, and contradictory, the overexpression of N-RAS was present [34]. It shows there may be an association between the expression levels of miR-98 and N-RAS. Further, to examine the roles of miR-98 in the expression of N-RAS, ACC-M cells were transfected with miR-98 mimics and control [34]. The results obtained from western blotting showed upregulation of miR-98 (55-folds) after transfection. Concurrently, in miR-98-transfected cells, N-RAS expression was drastically reduced. Immunofluorescence assay results indicated that in miR-98-transfected cells, N-RAS was exhibited in the cytoplasm, and the fluorescence signal was reduced [34]. These findings suggest that miR-98 influences

N-RAS expression in a negative manner. A luciferase reporter analysis was carried out in 293T cells to check whether miR-98 regulates N-RAS expression directly [34]. The results indicate that luciferase activity significantly reduced luciferase activity in wild-type groups in the cells transfected with miR-98 mimics. However, no significant differences were seen between the mutant-type groups [34].

Furthermore, N-RAS expression was observed to correlate to clinical stage directly and tumor size irrespective of the age, sex, tumor histotype, and lymph node metastasis of tumor patients [34]. Next, MTT and colony formation assays were performed to check the effects of the miR-98 expressions on cell proliferation. The results indicated that higher expressions of miR-98 reduced cell viability and clonogenicity. In addition, they performed chemotaxis and wound healing assays to detect the roles of miR-98 in SACC. The results suggested that the percentage of migrating miR-98 transfected cells is notably less than in control groups [34]. Similar results were obtained in the transwell invasion assay as the percentage of miR-98 transfected cells invaded via Matrigel® was lower than those of control cell groups [34].

Moreover, expression levels of metastatic genes were also evaluated, and it was reported that in the miR-98-transfected cells, E-cadherin was increased, while N-cadherin and vimentin were decreased. These findings suggest that miR-98 may suppress migration and invasion in ACC-M cells. Furthermore, they analyzed the effects of miR-98 overexpression on thePI3K/ AKT and RAS/MAPK/ERK pathways to investigate the function of N-RAS metastasis and cell proliferation. In miR-98 transfected cells, p-AKT and p-ERK expression levels were lower compared to control cells [34]. Although, the expression levels of ERK1/2 and AKT were not different. Hence, these findings indicate that miR-98 may inhibit tumor cell proliferation and metastasis via regulating PI3K/ AKT and RAS/MAPK/ERK pathways, as demonstrated in Fig. 5 and Table 2 [34].

In conclusion, we observe that miR-98 operates as a tumor suppressor in SACC via targeting N-RAS. Its downregulation is linked with increased cell proliferation, metastasis, and clonogenicity, as seen in SACC. The higher expression of miR-98 inhibits cell proliferation and metastasis by regulating various signaling pathways, including PI3K/ AKT and RAS/MAPK/ERK. Thus, miR-98 can act as a prognostic and diagnostic biomarker, and miR-98-based therapy can reduce tumor proliferation and metastasis and can be used to treat SACC patients.

miR-125a-5p

miR-125a-5p is a 24 nucleotide long non-coding RNA located at chromosome 19q13.41. Various studies reported miR-125a-5p function in cell differentiation and its role as a tumor suppressor in different cancers (Fig. 4), in breast cancer via targeting *HDAC4* [115], in glioblastoma via targeting *TAZ* [116], in GC via targeting *ERBB2* [117] and in HCC via targeting *MMP11* and *VEGF* [118].

Liang et al. demonstrated *in-vitro* that the downregulation of miR-125a-5p enhances SACC cell motility and invasion. In addition, they also found that miR-125a-5p downregulation is linked to metastasis and poor prognosis in SACC patients [35]. To determine the role of miRNAs in SACC proliferation and development, researchers compared the expression levels of different miRNAs in human SACC cell lines SACC-83, SACC-LM, and SACC-LM$^{\mathbf{TGF\beta}}$ using miRNA microarrays, and the results revealed that the expression levels of 12 miRNAs differed significantly between SACC-83, SACC-LM, and SACC-LM$^{\mathbf{TGF\beta}}$ cells [35]. In addition, qRT-PCR was also used to confirm the expression differences in the 12 miRNAs, and in comparison, to SACC-83 cells, miR-125a-5p was shown to be down-regulated in SACC-LM and SACC-LM$^{\mathbf{TGF\beta}}$ cells [35]. To evaluate the expression of miR-125a-5p in SACC tissues, qPCR was done in 8 samples of paired primary SACC tissues and ANTs [35]. qPCR results showed that the downregulation of miR-125a-5 was linked to an aggressive phenotype in SACC tissue. Target prediction software was used to identify the target, and *p38* was identified as a target gene of miR-125a-5p [35]. Luciferase reporter assays were also used to validate if *p38* is a target of miR-125a-5p. To delve deeper into the clinicopathological and prognostic importance of miR-125a-5p, its expression was identified in SACC patients and found that miR-125a-5p inhibition activated downstream p38/JNK/ERK pathways, as depicted in Fig. 5 and Table 2 [35].

These findings suggest that lower expression of miR-125a-5p enhances SACC development via regulating the p38 signaling pathway and that miR-125a-5p might be a valuable therapeutic target for SACC with antitumor properties.

miR-143-3p

miR-143-3p is a 21-nucleotide long miRNA located on chromosome location 5q32. Several research teams have investigated the role of miR-143-3p in carcinogenesis and tumor growth, and their findings suggest that miR-143-3p may operate as a tumor suppressor (Fig. 4) [119–121]. miR-143-3p is overexpressed in H. pylori-positive GC, and it has been shown to inhibit tumor proliferation, migration, and invasion by directly targeting *AKT2* [119]. However, in esophageal squamous cell carcinoma (ESCC) and ovarian carcinoma, miR-143-3p downregulation is related to cancer proliferation [36].

Various studies have shown that long non-coding RNAs (lncRNAs) can function as miRNA sponges, modulating endogenous miRNAs to target mRNAs and inhibiting their activity field[122]. Xie et al. demonstrated that ADAM metallopeptidase with thrombospondin type 1 motif, 9 (ADAMTS9) antisense RNA 2 (ADAMTS9-AS2) binds to miR-143-3p and suppresses its expression [36]. They also identified the signaling cascade, including lncRNA ADAMTS9-AS2 and miR-143-3p, that affected ITGA6 expression as well as the activity of PI3K/Akt and MEK/ERK signaling, controlling SACC cell migration and invasion [36]. Further, they demonstrated that by using a miRNA inhibitor to reduce elevated miR-143-3p expression, biological processes induced by ADAMTS9-AS2 knockdown were abolished, indicating that miR-143-3p is considered necessary for ADAMTS9-AS2-mediated regulation of ITGA6 and downstream PI3K/Akt and MEK/ERK signaling, which contribute to SACC cell migration and invasion (Fig. 5 and Table 2) [36].

In conclusion, we can say that by competing with miR-143-3p, ADAMTS9-AS2 increases migration and invasion in SACC. Thus, miR-143-3p can be used for its antitumor property and ADAMTS9-AS2 gene silencing for therapeutic purposes in SACC.

miR-187

miR-187 is synthesized from its precursor form miR-187 located on chromosome location 18q12.2. miR-187 plays both oncogenic as well as tumor suppressor roles (Fig. 3) in various cancers, for example, in NSCLC as a tumor suppressor by targeting Fibroblast Growth Factor 9 (FGF9) [123] and as an oncogene in ovarian cancer in which miR-187 overexpression leads to tumor proliferation by disabled homolog (DAB2) [124]. In addition, Hu et al. found that Increased expression of circRNA_0001283 reduced miR-187-induced breast cancer cell invasion [125].

A recent study done by Zhang et al. found that C-X-C chemokine receptor type 5 (CXCR5) induces tumor cell differentiation into Schwann-like cells by suppressing miR-187, which disinhibited S100 Calcium Binding Protein A4 (S100A4)and hence facilitated SACC perineural invasion (PNI) [37]. To understand the involvement of miRNA in CXCR5-induced PNI of SACC, researchers used miRNA array analysis and TargetScan to anticipate possible target relationships. They identified that miR-187, which contains S100A4 binding sites, was the highest upregulated miRNA following the CXCR5 deletion [37]. Dual-luciferase reporter assays and rescue tests also showed that miR-187 silencing was used to depress S100A4 expression, resulting in CXCR5-dependent regulation of PNI. S100A4 overexpression might counteract the inhibitory impact of CXCR5 knockdown of miR-187 overexpression on migration, invasion, and PNI (Fig. 5 and Table 2) [37].

To summarize, CXCR5 facilitates PNI by downregulating miR-187, which inhibits S100A4 expression in SACC. Thus, miR-187 could be a diagnostic and therapeutic biomarker with antitumor properties.

Other dysregulated miRNAs in SACC

Many researchers performed miRNA expression profiling to understand the value of miRNA in SACC progression and found many differentially expressed miRNAs; some were validated, and others are still to be investigated. Among these studies, Mitani et al. found that the miR-17-92 clusters, especially miR-17 and miR-20a, were significantly upregulated and were also significantly correlated with poor survival [126]. Additionally, miR-375, miR-155, miR-33b, miR-148, miR-142-5p, miR-142-3p, and miR-29 family were downregulated in SACC; they also validated miR-375 to be downregulated in SACC tissues by qRT-PCR and more studies still awaits. Afterward, Chen et al. used qPCR to validate the microarray results and confirmed the upregulated expression of miR-4487, miR-4430, and miR-486-3p and downregulated expression of miR-5191, miR-3131, and miR-211-3p, associated with SACC metastasis [127]. Kiss et al. identified that Let-7b, let-7c, miR-17, miR-20a, miR-24, and miR-195 were overexpressed in salivary gland-derived tumors compared to normal ones [128]. In another study using miRNA profiling, Kiss et al. found that let-7b and miR-193b were downregulated in SACC compared to adjacent standard tissue [129]. Feng et al. reported that miR-99a is highly expressed in SACC-LM cell lines, and *UBA2* is found to be the target gene in the SACC tissues [22]. Next, Andreasen et al. presented a cohort study in which they found three miR-21, miR-181a-2, and miR-152 to be highly expressed and correlated with poor overall survival [130]. As miR-21 has already been studied in quite a detail, more study is needed for miR-181a-2 and miR-152. On the other hand, five miRNAs were downregulated, including miR-138-5p, miR-148a-5p, miR-885-5p, miR-329-3p, and miR-29c-3p [130]. Zhao et al. studied miR-338-3p, which acts as a tumor suppressor in SACC, and reported that when hsa_circ_0059655 (oncogene) was knocked down, the expression of miR-338-3p was upregulated. In contrast, target gene *CCND1* (oncogene) expression was reduced, which was consistent with competing endogenous (ceRNA) expression patterns. This indicates that hsa_circ_0059655 / miR-338-3p / *CCND1* may have a role in the onset and progression of SACC, thus offering a fresh perspective on research concerning SACC [131]. Further, Han et al. also reported low expression of miR-885-5p (tumor suppressor) that targets *SCUBE3* (oncogene) in SACC, and it may have an essential role in EMT, which is a crucial process in lung metastasis of SACC [132]. Wang et al. found that miRNAs derived from the same precursor may share one or more common targets like miR-338-5p/3p and inhibits ACC-M and MDA-MB-231 cell motility and invasion by targeting LAMC2 [133]. Han et al. studied the correlation between circRNA and miRNA, and they found that circRNA_ABCA13 (ATP-binding cassette sub-family A member 13) may enhance the development and progression of SACC by inhibiting miR-138-5p activity [134]. Ju et al. identified that by modulating the expression level of hsa_circRNA_001982, the expression of miR-181a-5p may be changed, which affects the migration and invasion of SACC cells. The interaction between hsa_circRNA_001982/miR-181a-5p may be associated with distant SACC metastasis, and hsa_circRNA_001982 and miR-181a-5p may operate as a novel potential SACC biomarker [135]. A study by Zhu et al. reported that miR-331-3p was associated with anillin actin-binding protein (ANLN) and centromere protein F (CENPF), implying that miR-331-3p may influence the phenotype of SACC by promoting the expression of ANLN and CENPF [136]. These miRNAs are dysregulated in SACC, but the pathways and mechanisms are unknown. More research is needed to understand the mechanisms of these dysregulated miRNAs. Future research will uncover new biomarkers for the diagnosis and treatment of SACC.

Conclusion and future perspective

Due to high metastasis and a high recurrence even after surgery, SACC is a type of rare salivary gland cancer with a meager disease-free survival. Effective treatment against SACC's progression to recurrent metastatic disease is very challenging. The upregulation of many marker proteins, such as SOX, VEGF, EGFR, and MYB, has been demonstrated in SACC. However, in the clinical trials, pathways associated with these proteins failed. Therefore, there is a need to find other novel molecules that can be used as biomarkers for diagnostic/prognostic and therapeutic purposes.

In this regard, the discovery of miRNAs has opened up new possibilities in gene regulation, as carcinogenesis is thought to be influenced by several differentially expressed miRNAs. By inhibiting a large number of genes simultaneously, miRNAs at the later stages of differentiation may help keep cells differentiated. Many miRNAs and their target molecules have been shown to play an important role in the growth and spread of SACC, as miRNAs can act as tumor suppressors or oncogenic in various malignancies. Moreover, miRNA can have dual role in a cancer type which further tells us about the specificity of miRNAs as dual role of these miRNA may depend upon race, ethnicty, and other clincopathological characteristics of the patients [17]. miRNAs are easily quantifiable using polymerase chain reaction methods, making them a good candidate for diagnostic/prognostic monitoring of cancers. Thus, using miRNAs as predictive biomarkers and therapeutic targets has recently become one of the fascinating elements of cancer research. Although, targeting of miRNA with dual nature may not be possible for therapy purposes as they can cause toxicity to both normal and tumor cells. A greater investigation of microRNA profiling in a broader range of cancer types could provide insight into developing faster and more cost-effective cancer and drug resistance detection systems that can cut healthcare time and costs. In recent years, novel *in silico* design methodologies for developing artificial microRNAs has been established, giving a cutting-edge to miRNA cancer therapy. Cancer medication therapy has improved patient survival and reduced mortality rates recently. On the other hand, new molecular targets with greater cancer subtype specificity are needed. Despite the lack of defined guidelines for the applicability of miRNAs in current clinical practice, intriguing data suggest their future use. miRNAs are approachable as they are readily identified from blood, urine, and other body fluids using liquid biopsies. They have high sensitivity and specificity, the major requirements for an ideal clinical biomarker. miRNAs can have tumorigenic or suppressive effects on SACC cells, as is the case in all types of malignancies that have been explored. Identifying which miRNAs are involved in SACC and what function they serve will not only aid in the accurate diagnosis of the condition and risk assessment of patients, but it might also help develop novel therapeutics.

The first possible application of microRNAs in cancer is the reintroduction of a single or many mimic microRNAs (non-natural double-stranded miRNA-like RNA fragments) into a group of tumor cells, intending to restore a loss-of-function gene.

Regarding the approaches in therapeutics of cancer to date, potential avenues for accelerating the development of anticancer drugs have emerged and aided a new paradigm in targeting specific cancer types. Targeting the dynamic changes in the oncogenic factors, such as circRNAs, could act as potential biomarkers for cancer type-specific diagnosis, prognosis, and treatment monitoring [137]. Moreover, the discovery of hypoxia-inducible factor-1 (HIF-1) inhibitors derived from natural compounds like Acriflavine, Gliotoxins, Bavachinins [138], and another anticancer drug named Resveratrol (3,4',5-trihydroxy-trans-stilbene), a plant produced natural phytoalexin, are expected to be on their way to get used in clinical trials with cancer-treating effects. But the primary hurdles for using these appear to be their poor bioavailability and low efficacy. Additionally, the nephrotoxicity that resveratrol causes in individuals with multiple myeloma restrict its future advancement as an anticancer medication [139].

This review primarily focuses on the future application of these miRNAs as novel diagnostic, predictive biomarkers, and therapeutic targets that can be used in therapies (Tables 1 and 2). We also compiled many differentially expressed miRNAs that might be useful in future research to confirm their functions in SACC progression and metastasis.

Limitations

In the present study, we presented the role of miRNAs in SACC development and progression. We found that dysregulation in expression levels of miRNA plays a crucial role in the pathological progression of SACC. In most cases, SACC cells exhibit a distinct miRNA expression pattern related to a particular cancer phenotype. Mechanistically, it was observed that these miRNAs regulate several gene expressions or participate in more than one signaling pathway in cancer cells. But compared to their role in cancer progression, their application in therapeutics is minimal, and there are various challenges to overcome before reaching clinical stages. Like during our study, we also observed that the dysregulated miRNAs playing a role in SACC are not only specific to this cancer type but are also seen to be expressed aberrantly in some other cancer forms. Further, some miRNAs function as tumors promoting and tumor-suppressing molecules in the same cancer type as in SACC. Considering all these aspects, miRNA research must go a long way to evaluate them as specific biomarkers or therapeutic targets for a cancer type, such as in SACC.

Besides this, in therapeutics, miRNA delivery to tumor cells needs specificity, improved half-life, bio-distribution, and increased circulation around the tumor environment. To deal with this, various lipid-based nanoparticles (LBNP), such as nanostructured lipid carriers and liposomes, can be used for targeted delivery of therapeutic miRNAs to increase their stability and specificity in the tumor microenvironment.

Despite various challenges, miRNA like miR-34a mimic (MRX34) related to liver cancer is in phase-I clinical trials [140]. In contrast, testing miRNA in urine samples for the detection of endometrial cancer has also shown promising results in clinical trials (NCT Number-NCT03824613). Furthermore, a recent study was also conducted to evaluate the diagnostic accuracy of using salivary miRNAs from the salivary extracellular vesicles to detect the malignant transformation of the premalignant lesions using the qRT-PCR analysis (NCT Number- NCT04913545). Therefore, we are hopeful that some of the miRNAs mentioned above having a significant role in SACC carcinogenesis also be considered for clinical trials soon.

Author contributions

A.J. conceived the idea and did the final editing. P.K, R.K.K, and V.U wrote the manuscript. A.B, M.R and N.S did proofreading and checked readability. T.S.B and U.S made the figures and tables. All the authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

All the authors declared that they have no known conflict of interest that could have appeared to influence the work reported in this paper.

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