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Regulatory role of circular RNAs in oral squamous cell carcinoma

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ABSTRACT

OSCC is a genomically complicated disease and advancements in the modern era of molecular oncology have enabled researchers to portray near-to-complete resolution of signaling landscape. Over the last two decades, overwhelming proof-of-concept has established mechanistic regulatory role of non-coding RNAs in carcinogenesis, including OSCC. Circular RNAs demonstrate a burgeoning facet of oncology research and molecular biologists are only beginning to appreciate and recognize the significance of circRNAs in the pathogenesis of OSCC. Regulatory roles of non-coding RNAs in the re-shaping of signaling pathways offer plausible strategies for prevention/inhibition of OSCC. Circular RNAs have mechanistic roles in OSCC and "sponge effects" mediated by a wider variety of circRNAs need to be rationally targeted for effective cancer prevention. Phenomenal and cutting-edge research works in different types of animal models will further refine our knowledge for selection of most promising circRNAs as pharmacologically valuable targets.

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Introduction

Development of highly efficient therapeutic strategies tailored to patients with oral squamous cell carcinoma (OSCC) remains an overarching goal and pressing challenge (1-2). It is essential to mention that signal transduction cascades play instrumental role in the onset and progression of cancer. Deregulation of cell signaling pathways resulted in the loss of apoptosis, development of drug resistance, epithelial-to-mesenchymal transition and invasion of cancer cells (3-7).

Seminal research works related to the underlying mechanisms of carcinogenesis have emphasized on protein-coding genes mainly because proteins were classically viewed as the central dogma of molecular biology. Discovery of microRNAs (miRNAs) and long non-coding RNAs (LncRNAs) has generated wealth of evidence related to central role of non-coding RNAs in cellular functions and gene regulatory networks (8-17). Understanding the roles of lncRNAs and how they function in dynamic assemblies with other macromolecules has provided a better overview of regulatory role of lncRNAs during carcinogenesis and metastasis (18).

Notably, high-throughput transcriptomic studies in the last two decades have unraveled rapidly expanding list of non-coding RNAs that outnumber the protein encoding genes within the human genome.

Circular RNAs were identified initially in RNA viruses and considered transcriptional background noise. However, with rapid advancements in molecular biology, use of bioinformatics approaches and high-throughput RNA sequencing technologies, researchers were able to structurally and functionally characterize circRNAs. Linear pre-mRNAs generate circRNAs through back-splicing or skipping of exons. Importantly, circular form of circRNAs protected them from degradation by exonucleases and made them significantly stable (19-22). Essentially, circRNAs hold a great potential with reference to therapeutic applications for OSCC, either through inhibition or restoration of circRNAs that fine-tune cancer cells' regulatory networks (23-25).

In this review we have summarized most exciting findings related to regulation of cell signaling pathways by circular RNAs in various cancers.

Regulation of Signaling Proteins by Circular RNAs

Gleaning knowledge from different facets of molecular biology has enabled researchers to systematically characterize cell signaling pathways and integrate them into discrete structure-function-based systems in context of different diseases (26-35).

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E-cadherin was found to be enhanced whereas, levels of N-cadherin and Vimentin were noted to be reduced in circZDBF2-silenced-SCC9 and SCC15 cells (36). Circ-ZDBF2 antagonized miR-500b-5p and miR-362-5p mediated targeting of RNF145. CEBPB (CCAAT enhancer binding protein beta) has been shown to transcriptionally upregulate RNF145. circZDBF2 effectively promoted the binding of CEBPB to promoter regions of RNF145 (figure 1). Consequently, RNF145 activated NFκB to transcriptionally upregulate IL-8 in OSCC cells. There was evident tumor regression in mice inoculated with circZDBF2-silenced-OSCC cells (36).

SP1 transcriptionally upregulated the expression of circFAM126A in OSCC cells (37). circFAM126A blocked miR-186-mediated inhibition of FUS. circFAM126A interacted with RNA-binding protein FUS to promote mRNA stability of RAB41. circFAM126A knockdown caused significant decrease in the tumor size, volume and liver metastasis (37).

Knockdown of circ_0005320 resulted in the inhibition of phosphorylation of JAK2 and STAT3, which were abolished by the introduction of miR-486-3p inhibitors or miR-637 inhibitors in SCC25 and CAL27 cells (38). circ_0005320 levels were reduced, while the levels of miR-637 as well as miR-486-3p were noted to be increased in the tumor tissues of sh-circ_0005320 groups (38).

ZNF460 (Zinc Finger Protein 460) has the ability to transcriptionally upregulate circMTO1. Consequently, circMTO1 antagonized miR-320a-mediated inhibition of ATRX. circMTO1 knockdown reduced migration and invasion of OSCC cells (39).

Impairment of autophagy results in aggregation of p62. Circ-PKD2 overexpression potently enhanced autophagy as evidenced by considerable increase in LC3-II to LC3-I ratio and simultaneous reduction in the levels of p62 (40). Circ-PKD2 overexpression led to an increase in the accumulation of autophagic vesicles in cisplatin-treated-SCC-15 and CAL-27 cells. The nutrient-sensing kinase mTOR inhibits the activation of autophagy primarily through blockade of the assembly of ATG1-ATG13-ATG17 complexes through hyper-phosphorylation of ATG13. Circ-PKD2 interfered with miR-646-mediated targeting of ATG13. Knockdown of ATG13 markedly reduced caspase-8 activity induced by circ-PKD2 overexpression. circ-PKD2 induced significant increase in the activity of caspase-8 and caspase-3 in cisplatin-treated OSCC cells but these effects were attenuated by ATG13 silencing and miR-646 mimics. circ-PKD2 overexpression triggered significant increase in the chemo-sensitivity. Furthermore, tumor mass derived from circ-PKD2 overexpressing OSCC cells was smaller in size (40).

Circ-PKD2 sequestered away miR-204-3p and potentiated the expression of APC2 (adenomatous polyposis coli 2). Overexpression of miR-204-3p stimulated the levels of β-catenin, p-AKT and p-ERK1/2 in OSCC cells. Tumor growth was noticed to be remarkably impaired in mice injected subcutaneously with circ-PKD2-overexpressing SCC-15 cells (41).

Malignant tumors have characteristically exceptional features to disseminate through lymphatic vessels to lymph nodes. Studies have shown that tumors produce different growth factors that directly or indirectly stimulate

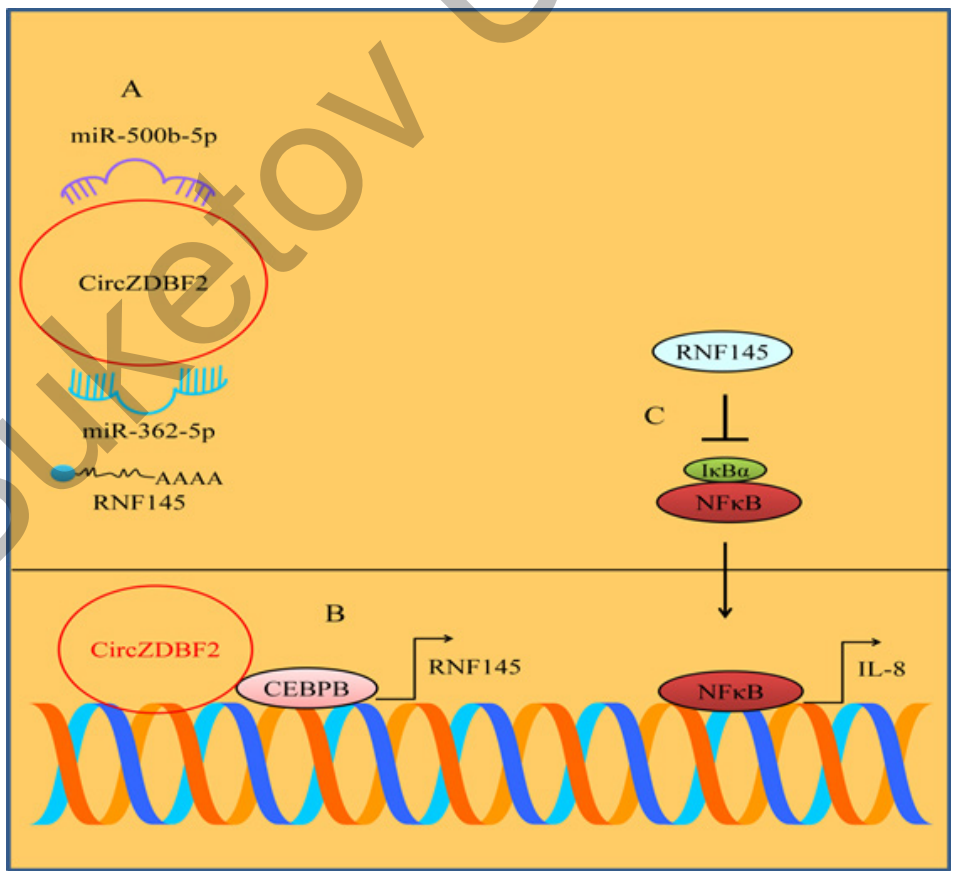

Figure 1. Sponge effects and circRNA-mediated transcriptional upregulation of cancer-associated genes. (A) CircZDBF2 antagonized miR-500b-5p and miR-362-5p mediated targeting of RNF145. (B) CircRNA worked with CEBPB and stimulated the expression of RNF145. (C) RNF145 enhanced the degradation of IκBα and activated NFκB. Consequently, activated NFκB moved into the nucleus and transcriptionally upregulated IL-8.

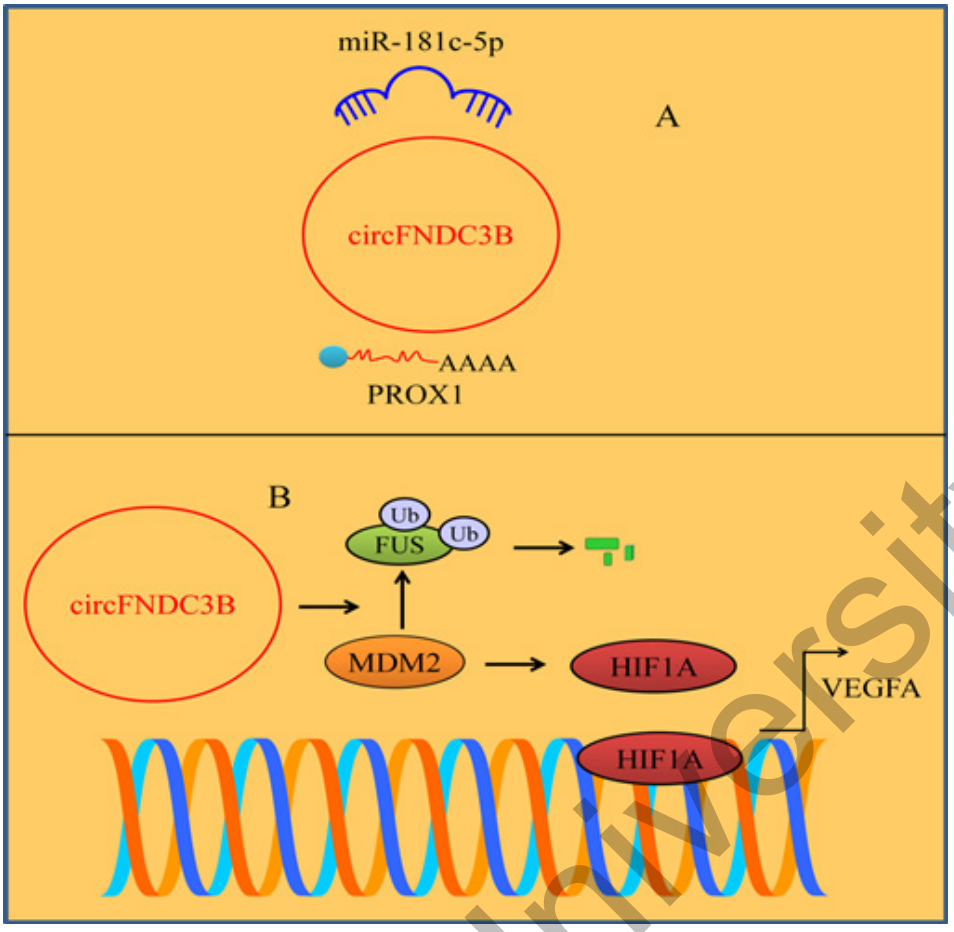

Figure 2. Role of circFNDC3B in progression of OSCC. (A) circFNDC3B interfered with miR-181c-5p-mediated inhibition of PROX1. (B) circFNDC3B promoted MDM2-mediated degradation of FUS protein. MDM2 increased the stability of HIF1A. Sequentially, HIF1A transcriptionally upregulated VEGFA and promoted carcinogenesis.

the growth of lymphatic vessels (lymphangiogenesis) and lymphatic metastasis.

Circular RNAs have been reported to modulate an array of proteins via ubiquitination-mediated degradation. circFNDC3B promoted proteasome-dependent degradation of FUS. Mechanistically, circFNDC3B enhanced the interaction of MDM2 (murine double minute 2) and FUS (Figure 2). However, interaction between MDM2 and FUS was found to be reduced in circFNDC3B-depleted cells. MDM2 not only stabilized HIF1A but also promoted HIF1A-mediated transcriptional upregulation of VEGFA. MDM2 overexpression led to inhibition of HIF1A ubiquitination in 293T cells. circFNDC3B interfered with miR-181c-5p-mediated inhibition of PROX1 (Figure 2). PROX1 is a versatile transcriptional regulator as it centrally drives lymphangiogenesis and growth of the lymphatic endothelial cells, whereas ESM1 modulates the lymphangiogenic processes. Knockdown of circFNDC3B was reported to be associated with a lower LN volume, whereas its overexpression increased LN micrometastases. circFNDC3B proficiently enhances the metastasizing abilities of OSCC by promoting angiogenesis/lymphangiogenesis in metastatic tumor microenvironment (42). Next-generation lymphatic targeting options can be tested in animal models to improve our understanding of changes in lymphatic structures and functions to promote pharmaceutical targeting of the lymphatics.

Regression of the malignant tumors was noted in experimental mice inoculated with circ_OSBPL10-silenced-SCC-9 cells. circ_OSBPL10 downregulation led to an increase in miR-299-3p and a simultaneous decrease in CDK6 levels in the tumor xenografts (43).

hsa_circ_0060927 interacted with miR-195-5p and caused blockade of miR-195-5p-mediated targeting of TRIM14 (Tripartite Motif Containing 14). hsa_circ_0060927 overexpression enhanced the proliferative and migratory phenotype of OSCC cells (44).

circ-CLK1 inhibited the apoptotic death of OSCC cells by suppression of miR-18b-5p-mediated targeting of YBX2 (Y-box protein 2) (45).

Regulation of EZH2 by CircRNAs and LncRNAs

EZH2, a histone methyltransferase subunit of a Polycomb repressor complex has an imperative role as a master regulator of transcription (46-49).

EZH2 catalyzed the addition of methyl groups to histone H3 at lysine 27 and promoted carcinogenesis. HOTAIR, a long non-coding RNA promotes invasion and metastasis by promoting the recruitment of EZH2 to the promoter region of E-cadherin in oral squamous cell carcinoma (50). circ_0000311 interfered with miR-876-5p-mediated targeting of EZH2. circ_0000311 knockdown impeded the proliferation and epithelial-mesenchymal transition (EMT) of OSCC cells (51).

FUS (fused in sarcoma/translocated in liposarcoma), an RNA binding protein has been shown to interact with long non-coding RNA PART1 (Prostatic androgen-regulated transcription-1) to stabilize EZH2. Importantly, tumors derived from PART1-silenced CAL27 cells demonstrated

notable reduction in the levels of PART1 and EZH2 (52).

The growing insight into non-coding RNA-mediated control of EZH2 has opened new avenues for therapeutic targeting.

Regulation of Immunological Responses

Regulatory T cells (Tregs) are specialized T cells having unique ability to suppress immunological responses. hsa_circ_0069313 interfered with miR-325-3p-mediated targeting of FOXP3 in OSCC cells. Exosomally transferred hsa_circ_0069313 promoted the functions of regulatory T cells primarily through increase in FOXP3 levels (53). Functionally active Tregs efficiently suppressed the immunological response against cancer cells.

PD-1 blockade triggers the expansion of $CD8^+$ T cells in the tumor microenvironment. $CD8^+$ T cells are differentiated into short-lived cytolytic $CD8^+$ T cells in response to inflammatory cytokines. CircKRT1 inhibited miR-495-3p-mediated targeting of PD-L1 in OSCC cells. Co-culture of $CD8^+$ T cells with circKRT1-silenced-CAL-27 or HSC-3 cells caused significant increase in cytotoxicity of $CD8^+$ T cells against OSCC cells. CircKRT1 knockdown enhanced cytotoxic effects and inhibited the apoptotic death of $CD8^+$ T cells (54).

Camrelizumab with docetaxel/cisplatin is currently being considered as a first-line therapy. The combinatorial regime has been reported to be well-tolerated and demonstrated remarkable efficiency in PD-L1-positive patients with recurrent/metastatic oral squamous cell carcinoma (55).

Regulation of Hippo Pathway by CircRNAs

Emerging interest in the components of Hippo pathway has generated a wealth of exciting scientific knowledge (56-59). LATS2 (Large Tumor Suppressor Kinase-2) mediated phosphorylation of YAP1 inhibited its nuclear accumulation (60). miR-31 targets LATS2 and activates Hippo pathway in OSCC cells. However, circRNA_0000140 suppressed miR-31-mediated targeting of LATS2 in OSCC cells. There was an evident accumulation of YAP1 in the nucleus in miR-31-overexpressing OSCC cells. LATS2 knockdown led to suppression in the levels of E-cadherin along with a significant increase in the levels of N-cadherin, vimentin, matrix metalloproteinases (MMP-2 and MMP-9). circ_0000140 inhibited tumor formation and metastatic spread of OSCC cells by blockade of miR-31-mediated targeting of LATS2 (61). Overall, these findings are interesting and targeted inhibition of Hippo pathway will be valuable in the treatment of OSCC. Better comprehension of the connections between the Hippo pathway and its upstream signals will provide novel perspectives related to pharmacological targeting of Hippo pathway.

Regulation of TGF/SMAD Pathway by CircRNAs

How TGF/SMAD signaling integrates numerous cues and translates them into specific downstream responses is an exciting dimension with major implications for our concepts related to the physiology and disease mechanisms (62-66).

circUHRF1 interfered with miR-526b-5p-mediated targeting of c-Myc in SCC25 and CAL27 cancer cells. ESRP1 (Epithelial splicing regulatory protein 1) promoted the circularization and biogenesis of circUHRF1. c-Myc transcriptionally upregulated TGFβ1 and ESRP1 in OSCC cells. Multiplicity of pulmonary metastatic nodules was found to be substantially reduced in experimental mice injected with CircUHRF1-silenced-SCC25 cells (67).

circLDLRAD3 blocked miR-558-mediated targeting of SMAD4 in OSCC. Importantly, tumors derived from circLDLRAD3-overexpressing OSCC cells were smaller in size, while the tumors developed from circLDLRAD3-knockdown group presented larger size of the tumors. Essentially, the number of metastatic nodules on the surface of the lungs from circLDLRAD3-overexpressing group was noted to be significantly lower. Whereas, there was an increase in the number of metastatic nodules in mice injected with circLDLRAD3-knockdown OSCC cells (68).

circANKS1B potentiated the expression of TGFβ1 and interfered with miR-515-5pmediated targeting of TGFβ1. circANKS1B depletion not only increased cisplatin-sensitivity of OSCC cells but also induced apoptotic death (69).

Together, the complex mechanisms governing TGF/SMAD offer strategies to develop therapeutics that control invasion and metastatic spread of cancer cells.

m6A Modifications in Circular RNAs

In 2017, a research team spearheaded by Alan C. Mullen firstly reported the profile of m6A modifications on circRNAs through a computational pipeline (AutoCirc) tool. Utilizing the data of m6A methylated RNA immunoprecipitation sequencing and m6A-circRNAs microarray, research team demonstrated that m6A-circRNAs exhibited discrete modification styles in oral squamous cell carcinoma.

CircFOXK2 is derived principally from the Exon 3-2 of FOXK2 genome with 343 bp length (**70**). Moreover, in the adjacently located area of circFOXK2 conjunction site, m6A modification site has been identified within the GGACT site. Knockdown of circFOXK2 reduced the migratory properties of OSCC cells, whereas, overexpression of circFOXK2 fueled the migratory potential of cancer cells. Overall, circFOXK2 potently enhanced the malignant phenotype of oral squamous cell carcinoma cells. Furthermore, CircFOXK2 worked synchronously with IGF2BP3 and enhanced the stability of GLUT1 mRNA. Overexpression of circFOXK2 effectively promoted the interaction between IGF2BP3 and GLUT1, while knockdown of circFOXK2 caused severe dissociation of the interaction between IGF2BP3 and GLUT1. Collectively, these findings suggested that circFOXK2 effectively stabilized GLUT1 mRNA primarily through interaction with IGF2BP3 in m6 A-dependent manner (70).

Regulation of Histone Lysine Demethylases by CircRNAs

Deregulations of JmjC KDM (JmjC-domain-containing histone demethylase) family members have greater implications than previously anticipated. JmjC KDM family provides a therapeutic avenue for the treatment of cancers. Lysine-specific demethylases are increasingly being recognized as versatile regulators of invasion and progression of OSCC. KDM2A (Lysine demethylase

2A) is involved in the demethylation of the dimethylated H3K36 (H3K36me2) residue. Lysine-specific demethylase 4A (KDM4A) also known as Jumonji domain-containing protein 2A (JMJD2A) has also been shown to play major role in the progression of OSCC.

circFOXO3 potentiated the expression of KDM2A by relieving the repressive effects of miR-214 on KDM2A. circFOXO3 and KDM2A effectively promoted the growth of the OSCC cells (71). Use of miRNA-214 mimics can be an exciting opportunity to induce regression of the tumors in experimental mice.

Knockdown of circGOLPH3 inhibited malignant phenotype of OSCC cells. CircGOLPH3 efficiently inhibited miR-145-5p-mediated targeting of KDM2A. There was a significant regression of the palpable tumors in experimental mice inoculated with circGOLPH3-silenced-HSC-3 cells (72).

LEF1 not interacts with KDM4A but also guides the recruitment of KDM4A complexes to the chromatin. KDM4A suppression led to a substantial increment in the enrichment of H3K36me3 on the promoter region of LATS2. There was an evident reduction in the tumor-forming capacities of LEF1-silenced or KDM4A-silenced CAL-27 cancer cells (73).

Regulation of PI3K/AKT/mTOR Pathway

Wealth of information has greatly advanced our current conceptual understanding of the mechanistic basis for the involvement of phosphatidylinositol-3-kinases in diseases and assesses the preclinical and clinical breakthroughs related to phosphatidylinositol-3-kinases inhibitors (74-80). The state of the art in the regulation of PI3K/AKT signaling by circRNAs is discussed.

These emerging themes of intricate regulation of signaling pathways by circular RNAs have started to draw widespread attention. In this section, we have presented an overview related to the ongoing developments about the regulation of circular RNAs by PI3K/AKT pathway in OSCC.

circ_0058063 sponged miR-145-5p and activated the PI3K/AKT pathway in OSCC cells. miR-145-5p overexpression inhibited the phosphorylation of PI3K and AKT. There was an evident increase in the tumor mass in mice inoculated with circ_0058063-expressing-SCC-9 cells (81).

NUPR1 (Nuclear protein-1) played central role in the progression of OSCC. circHIPK3 interfered with miR-637-mediated inhibition of NUPR1. Levels of p-PI3K and p-AKT were found to be reduced in miR-637 mimics-treated OSCC cells. However, circHIPK3 overexpression triggered an increase in the levels of p-PI3K and p-AKT (82).

Similarly, LTBP2 (Latent Transforming Growth Factor-β-Binding protein 2) worked synchronously with CircEPSTI1 and promoted carcinogenesis. CircEPSTI1 sponged away miR-942-5p and potentiated the expression of LTBP2. PI3K/AKT/mTOR pathway was noted to be functionally active in circEPSTI1^{high}/miR-942-5p^{low} OSCC tissues. BEZ235 (PI3K/mTOR dual inhibitor) significantly reduced the size and weight of tumors derived from circEPSTI1-overexpressing CAL27 and SCC9 cells (83). Hypoxia activated p-AKT and p-ERK½ but downregulated the levels of p-mTOR. circCDR1as overexpressing-cells demonstrated higher ROS levels in hypoxic cells. There was a significant increase in the volume and weight of the tumors in mice inoculated with CircCDR1as-overexpressing Tca-8113 cells (84).

Importantly, circular RNAs also serve as tumor suppressors. hsa_circ_0007059 significantly inhibited the malignancy of OSCC cells. Essentially, hsa_circ_0007059 inactivated AKT/mTOR signaling pathway (85).

PI3K family is an efficient and medicinally valuable candidate for the development of small-molecule inhibitors, portending greater-than-ever potential as bona fide pharmacological targets. In line with this approach, highly selective and potent inhibitors have been developed for different members of PI3K family. Keeping in view the milestones set to design kinase-targeted antibodies as well as small-molecule inhibitors, combinatorial strategies consisting of synthetic oligonucleotides for inactivation of oncogenic circRNAs will be advantageous.

Concluding remarks

Importantly, discoveries of circRNA-miRNA regulatory axis in oral squamous cell carcinoma have been made through advancements in the microarray and sequencing platforms. Therefore, correlations between the identified and to-be-identified circRNAs should be further characterized by large-scale studies which will be valuable to superimpose the regulatory networks of multiple circular RNAs thus enabling interdisciplinary researchers to design personalized therapeutics for OSCC patients.

Author contributions

RA and MZQ conceived the idea. KN, MAR, UYS and IMY browsed the literature and prepared the initial draft. RA cross-checked the authenticity of the articles and made sure that most accurate references were shortlisted. KN, MAR, UYS and IMY made revisions. RA critically evaluated the revisions and edited the manuscript. MZQ designed the diagrams.

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