

## Regulatory role of circular RNAs in oral squamous cell carcinoma

Rukset Attar<sup>1\*</sup>, Khalida Noel<sup>2</sup>, Mirna Azalea Romero<sup>3</sup>, Uteuliyev Yerzhan Sabitaliyevich<sup>4</sup>,  
Ishmuratova Margarita Yulaevna<sup>5</sup>, Muhammad Zahid Qureshi<sup>6</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Yeditepe University Hospital, 34755 Istanbul, Turkey

<sup>2</sup>Human Anatomy Department, College of Medicine, Al-Mustansiriyah University, Baghdad, Iraq

<sup>3</sup>Facultad de Medicina, Universidad Autónoma de Guerrero, Laboratorio de Investigación Clínica, Av. Solidaridad S/N, Colonia Hornos Insurgentes, cp 39300, Acapulco, Guerrero México

<sup>4</sup>Scientific Center for Innovative Technologies and Research, Kazakhstan

<sup>5</sup>E. A. Buketov Karaganda University, Kazakhstan

<sup>6</sup>Deanship of Educational Services, Department of Biochemistry, Qassim University, Buraydah, Al Qassim, Buraidah 51452, Saudi Arabia

### ARTICLE INFO

#### Review

#### Article history:

Received: July 30, 2023

Accepted: August 20, 2023

Published: August 31, 2023

#### Keywords:

Oral Squamous cell carcinoma, Apoptosis, Metastasis, non-coding RNAs, circular RNAs

### 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.

Doi: <http://dx.doi.org/10.14715/cmb/2023.69.8.39>

Copyright: © 2023 by the C.M.B. Association. All rights reserved. 

### 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).

\* Corresponding author. Email: [ruksetattar@hotmail.com](mailto:ruksetattar@hotmail.com)

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 NF $\kappa$ B 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).

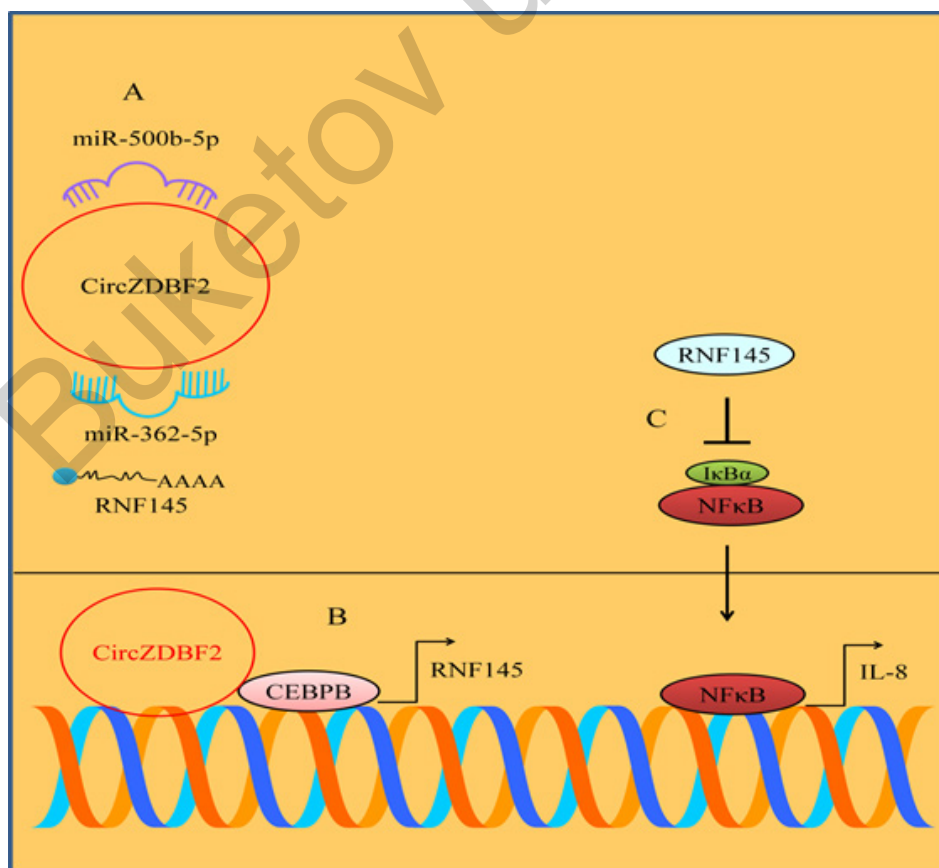
Knockdown of circ\_0005320 resulted in the inhibition of phosphorylation of JAK2 and STAT3, which were abolished by the introduction of miR-486-3p inhibitors or miR-637 inhibitors in SCC25 and CAL27 cells (38). circ\_0005320 levels were reduced, while the levels of miR-637 as well as miR-486-3p were 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).

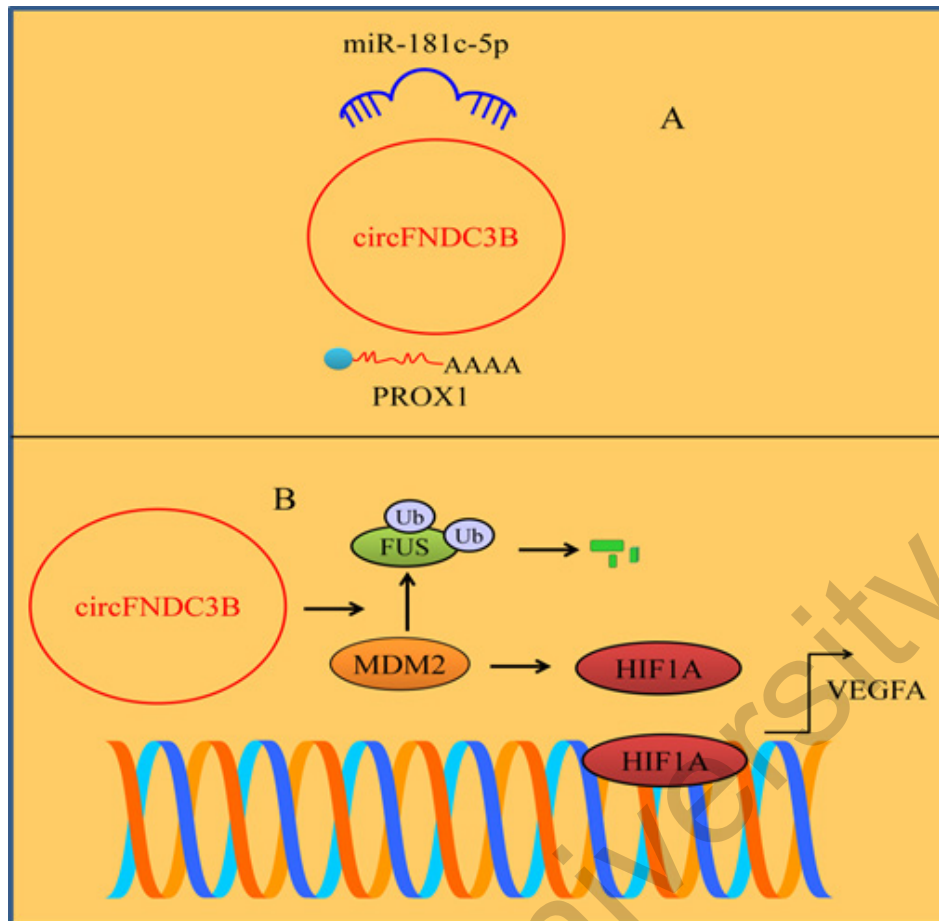
Impairment of autophagy results in aggregation of p62. Circ-PKD2 overexpression potently enhanced autophagy as evidenced by considerable increase in LC3-II to LC3-I ratio and simultaneous reduction in the levels of p62 (40). Circ-PKD2 overexpression led to an increase in the accumulation of autophagic 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  $\beta$ -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 I $\kappa$ B $\alpha$  and activated NF $\kappa$ B. Consequently, activated NF $\kappa$ B 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<sub>OSBPL10</sub>-silenced-SCC-9 cells. circ<sub>OSBPL10</sub> 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. HO-TAIR, 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<sup>+</sup> T cells in the tumor microenvironment. CD8<sup>+</sup> T cells are differentiated into short-lived cytolytic CD8<sup>+</sup> T cells in response to inflammatory cytokines. *CircKRT1* inhibited miR-495-3p-mediated targeting of PD-L1 in OSCC cells. Co-culture of CD8<sup>+</sup> T cells with *circKRT1*-silenced-CAL-27 or HSC-3 cells caused significant increase in cytotoxicity of CD8<sup>+</sup> T cells against OSCC cells. *CircKRT1* knockdown enhanced cytotoxic effects and inhibited the apoptotic death of CD8<sup>+</sup> 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-515-5p-mediated 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. Mulen 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* junction 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 m6A-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 (H3K36me<sub>2</sub>) 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 H3K36me<sub>3</sub> 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- $\beta$ -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<sup>high</sup>/miR-942-5p<sup>low</sup> 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-ERK $\frac{1}{2}$  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-over-expressing 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.

### References

- Ju WT, Xia RH, Zhu DW, Dou SJ, Zhu GP, Dong MJ, Wang LZ, Sun Q, Zhao TC, Zhou ZH, Liang SY, Huang YY, Tang Y, Wu SC, Xia J, Chen SQ, Bai YZ, Li J, Zhu Q, Zhong LP. A pilot study of neoadjuvant combination of anti-PD-1 camrelizumab and VEGFR2 inhibitor apatinib for locally advanced resectable oral squamous cell carcinoma. *Nat Commun.* 2022 Sep 14;13(1):5378. doi: 10.1038/s41467-022-33080-8.
- Zhao M, He Y, Zhu N, Song Y, Hu Q, Wang Z, Ni Y, Ding L. IL-33/ST2 signaling promotes constitutive and inductive PD-L1 expression and immune escape in oral squamous cell carcinoma. *Br J Cancer.* 2023 Mar;128(5):833-843. doi: 10.1038/s41416-022-02090-0.
- Zhao H, Li R, Chen Y, Yang X, Shang Z. Stromal nicotinamide N-methyltransferase orchestrates the crosstalk between fibroblasts and tumour cells in oral squamous cell carcinoma: evidence from patient-derived assembled organoids. *Oncogene.* 2023 Apr;42(15):1166-1180. doi: 10.1038/s41388-023-02642-5.
- Shriwas O, Arya R, Mohanty S, Mohapatra P, Kumar S, Rath R, Kaushik SR, Pahwa F, Murmu KC, Majumdar SKD, Muduly DK, Dixit A, Prasad P, Nanda RK, Dash R. RRBP1 rewires cisplatin resistance in oral squamous cell carcinoma by regulating Hippo pathway. *Br J Cancer.* 2021 Jun;124(12):2004-2016. doi: 10.1038/s41416-021-01336-7.

5. Omori H, Nishio M, Masuda M, Miyachi Y, Ueda F, Nakano T, Sato K, Mimori K, Taguchi K, Hikasa H, Nishina H, Tashiro H, Kiyono T, Mak TW, Nakao K, Nakagawa T, Maehama T, Suzuki A. YAP1 is a potent driver of the onset and progression of oral squamous cell carcinoma. *Sci Adv*. 2020 Mar 18;6(12):eaay3324. doi: 10.1126/sciadv.aay3324.
6. Hou Y, Yu W, Wu G, Wang Z, Leng S, Dong M, Li N, Chen L. Carcinogenesis promotion in oral squamous cell carcinoma: KDM4A complex-mediated gene transcriptional suppression by LEF1. *Cell Death Dis*. 2023 Aug 8;14(8):510. doi: 10.1038/s41419-023-06024-3.
7. Li Y, Li R, Qin H, He H, Li S. OTUB1's role in promoting OSCC development by stabilizing RACK1 involves cell proliferation, migration, invasion, and tumor-associated macrophage M1 polarization. *Cell Signal*. 2023 Oct;110:110835. doi: 10.1016/j.cell-sig.2023.110835.
8. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, Visone R, Iorio M, Roldo C, Ferracin M, Prueitt RL, Yanaihara N, Lanza G, Scarpa A, Vecchione A, Negrini M, Harris CC, Croce CM. A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc Natl Acad Sci U S A*. 2006 Feb 14;103(7):2257-61.
9. Lytle JR, Yario TA, Steitz JA. Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. *Proc Natl Acad Sci U S A*. 2007 Jun 5;104(23):9667-72.
10. Khraiweh B, Arif MA, Seumel GI, Ossowski S, Weigel D, Reski R, Frank W. Transcriptional control of gene expression by microRNAs. *Cell*. 2010 Jan 8;140(1):111-22.
11. Farhan M, Malik A, Ullah MF, Afaq S, Faisal M, Farooqi AA, Biersack B, Schobert R, Ahmad A. Garcinol Sensitizes NSCLC Cells to Standard Therapies by Regulating EMT-Modulating miRNAs. *Int J Mol Sci*. 2019 Feb 13;20(4):800. doi: 10.3390/ijms20040800.
12. Mytsyk Y, Dosenko V, Borys Y, Kucher A, Gazdikova K, Busseberg D, Caprnda M, Kruzliak P, Farooqi AA, Lubov M. MicroRNA-15a expression measured in urine samples as a potential biomarker of renal cell carcinoma. *Int Urol Nephrol*. 2018 May;50(5):851-859. doi: 10.1007/s11255-018-1841-x.
13. Farooqi AA, Kapanova G, Kalmakhanov S, Kussainov AZ, Datkhayeva Z. Regulation of Ferroptosis by Non-Coding RNAs: Mechanistic Insights. *J Pharmacol Exp Ther*. 2023 Jan;384(1):20-27. doi: 10.1124/jpet.121.001225.
14. Cabili MN, Dunagin MC, McClanahan PD, Biaesch A, Padovan-Merhar O, Regev A, Rinn JL, Raj A. Localization and abundance analysis of human lncRNAs at single-cell and single-molecule resolution. *Genome Biol*. 2015 Jan 29;16(1):20. doi: 10.1186/s13059-015-0586-4.
15. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, Poliakov A, Cao X, Dhanasekaran SM, Wu YM, Robinson DR, Beer DG, Feng FY, Iyer HK, Chinnaiyan AM. The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet*. 2015;47(3):199-208.
16. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL, Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature*. 2009;458(7235):223-7.
17. Chiu HS, Somvanshi S, Patel E, Chen TW, Singh VP, Zorman B, Patil SL, Pan Y, Chatterjee SS; Cancer Genome Atlas Research Network, Sood AK, Gunaratne PH, Sumazin P. Pan-Cancer Analysis of lncRNA Regulation Supports Their Targeting of Cancer Genes in Each Tumor Context. *Cell Rep*. 2018 Apr 3;23(1):297-312.e12.
18. Liu SJ, Dang HX, Lim DA, Feng FY, Maher CA. Long noncoding RNAs in cancer metastasis. *Nat Rev Cancer*. 2021 Jul;21(7):446-460. doi: 10.1038/s41568-021-00353-1.
19. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, Loewer A, Ziebold U, Landthaler M, Kocks C, le Noble F, Rajewsky N. Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature*. 2013 Mar 21;495(7441):333-8. doi: 10.1038/nature11928.
20. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. *Nature*. 2013 Mar 21;495(7441):384-8. doi: 10.1038/nature11993.
21. Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. *PLoS One*. 2012;7(2):e30733. doi: 10.1371/journal.pone.0030733.
22. Farooqi AA, Kapanova G, Kussainov AZ, Datkhayeva Z, Raganina K, Sadykov BN. Regulation of RASSF by non-coding RNAs in different cancers: RASSFs as masterminds of their own destiny as tumor suppressors and oncogenes. *Noncoding RNA Res*. 2022 May 13;7(2):123-131. doi: 10.1016/j.ncrna.2022.04.001.
23. Farooqi AA, Zahid R, Naureen H, Attar R, Gazouli M, Berardi R, Szlachowska J, Matkowski R, Pawlak E. Regulation of ROCK1/2 by long non-coding RNAs and circular RNAs in different cancer types. *Oncol Lett*. 2022 May;23(5):159. doi: 10.3892/ol.2022.13279.
24. Farooqi AA, Attar R, Yulaevna IM, Berardi R. Interaction of long non-coding RNAs and circular RNAs with microRNAs for the regulation of immunological responses in human cancers. *Semin Cell Dev Biol*. 2022 Apr;124:63-71. doi: 10.1016/j.semcdb.2021.05.029.
25. Farooqi AA, Naureen H, Attar R. Regulation of cell signaling pathways by circular RNAs and microRNAs in different cancers: Spotlight on Wnt/ $\beta$ -catenin, JAK/STAT, TGF/SMAD, SHH/GLI, NOTCH and Hippo pathways. *Semin Cell Dev Biol*. 2022 Apr;124:72-81. doi: 10.1016/j.semcdb.2021.04.002.
26. Celikkaya B, Durak T, Farooqi AA, Inci K, Tokgun PE, Tokgun O. The effects of MYC on exosomes derived from cancer cells in the context of breast cancer. *Chem Biol Drug Des*. 2023 Apr 29. doi: 10.1111/cbdd.14245.
27. Peng SY, Lin LC, Chen SR, Farooqi AA, Cheng YB, Tang JY, Chang HW. Pomegranate Extract (POMx) Induces Mitochondrial Dysfunction and Apoptosis of Oral Cancer Cells. *Antioxidants (Basel)*. 2021 Jul 13;10(7):1117. doi: 10.3390/antiox10071117.
28. Tian Y, Xu H, Farooq AA, Nie B, Chen X, Su S, Yuan R, Qiao G, Li C, Li X, Liu X, Lin X. Maslinic acid induces autophagy by down-regulating HSPA8 in pancreatic cancer cells. *Phytother Res*. 2018 Jul;32(7):1320-1331. doi: 10.1002/ptr.6064.
29. Farooqi AA, Rakhmetova V, Kapanova G, Mussakhanova A, Tashenova G, Tulebayeva A, Akhenbekova A, Xu B. Suppressive effects of bioactive herbal polysaccharides against different cancers: From mechanisms to translational advancements. *Phytomedicine*. 2023 Feb;110:154624. doi: 10.1016/j.phymed.2022.154624.
30. Katifelis H, Nikou MP, Mukha I, Vityuk N, Lagopati N, Piperi C, Farooqi AA, Pippa N, Efstathopoulos EP, Gazouli M. Ag/Au Bimetallic Nanoparticles Trigger Different Cell Death Pathways and Affect Damage Associated Molecular Pattern Release in Human Cell Lines. *Cancers (Basel)*. 2022 Mar 17;14(6):1546. doi: 10.3390/cancers14061546.
31. Farooqi AA, Rakhmetova VS, Kapanova G, Tashenova G, Tulebayeva A, Akhenbekova A, Ibekoven O, Turgambayeva A, Xu B.

- Bufalin-Mediated Regulation of Cell Signaling Pathways in Different Cancers: Spotlight on JAK/STAT, Wnt/ $\beta$ -Catenin, mTOR, TRAIL/TRAIL-R, and Non-Coding RNAs. *Molecules*. 2023 Feb 27;28(5):2231. doi: 10.3390/molecules28052231.
32. Naoum GE, Buchsbaum DJ, Tawadros F, Farooqi A, Arafat WO. Journey of TRAIL from Bench to Bedside and its Potential Role in Immuno-Oncology. *Oncol Rev*. 2017 Apr 28;11(1):332. doi: 10.4081/oncol.2017.332.
  33. Farooqi AA, Turgambayeva A, Tashenova G, Tulebayeva A, Bazarbayeva A, Kapanova G, Abzalievya S. Multifunctional Roles of Betulinic Acid in Cancer Chemoprevention: Spotlight on JAK/STAT, VEGF, EGF/EGFR, TRAIL/TRAIL-R, AKT/mTOR and Non-Coding RNAs in the Inhibition of Carcinogenesis and Metastasis. *Molecules*. 2022 Dec 21;28(1):67. doi: 10.3390/molecules28010067.
  34. Wang HR, Tang JY, Wang YY, Farooqi AA, Yen CY, Yuan SF, Huang HW, Chang HW. Manoalide Preferentially Provides Antiproliferation of Oral Cancer Cells by Oxidative Stress-Mediated Apoptosis and DNA Damage. *Cancers (Basel)*. 2019 Sep 4;11(9):1303. doi: 10.3390/cancers11091303.
  35. Datkhayev UM, Rakhmetova V, Shepetov AM, Kodasbayeva A, Datkayeva GM, Pazilov SB, Farooqi AA. Unraveling the Complex Web of Mechanistic Regulation of Versatile NEDD4 Family by Non-Coding RNAs in Carcinogenesis and Metastasis: From Cell Culture Studies to Animal Models. *Cancers (Basel)*. 2023 Aug 4;15(15):3971. doi: 10.3390/cancers15153971.
  36. Rong L, Chen B, Liu K, Liu B, He X, Liu J, Li J, He M, Zhu L, Liu K, Shi X, Shuai Y, Jin L. CircZDBF2 up-regulates RNF145 by ceRNA model and recruits CEBPB to accelerate oral squamous cell carcinoma progression via NF $\kappa$ B signaling pathway. *J Transl Med*. 2022 Apr 1;20(1):148. doi: 10.1186/s12967-022-03347-1.
  37. Wang J, Ouyang S, Zhao S, Zhang X, Cheng M, Fan X, Cai Y, Liao L. SP1-Mediated Upregulation of circFAM126A Promotes Proliferation and Epithelial-Mesenchymal Transition of Oral Squamous Cell Carcinoma via Regulation of RAB41. *Front Oncol*. 2022 Feb 14;12:715534. doi: 10.3389/fonc.2022.715534.
  38. Zheng X, Du F, Gong X, Xu P. Circ\_0005320 promotes oral squamous cell carcinoma tumorigenesis by sponging microRNA-486-3p and microRNA-637. *Bioengineered*. 2022 Jan;13(1):440-454. doi: 10.1080/21655979.2021.2009317.
  39. Zou C, Li X, Lv X, Wu S, Song J, Tang Z, Luo H, Wei H, Ai Y. Circular RNA mitochondrial translation optimization 1 homologue (CircMTO1) induced by zinc finger protein 460 (ZNF460) promotes oral squamous cell carcinoma progression through the microRNA miR-320a / alpha thalassemia/mental retardation, X-linked (ATRX) axis. *Bioengineered*. 2021 Dec;12(2):9585-9597. doi: 10.1080/21655979.2021.1997699.
  40. Gao L, Zhang Q, Li S, Zheng J, Ren W, Zhi K. Circ-PKD2 promotes Atg13-mediated autophagy by inhibiting miR-646 to increase the sensitivity of cisplatin in oral squamous cell carcinomas. *Cell Death Dis*. 2022 Feb 26;13(2):192. doi: 10.1038/s41419-021-04497-8.
  41. Gao L, Zhao C, Li S, Dou Z, Wang Q, Liu J, Ren W, Zhi K. circ-PKD2 inhibits carcinogenesis via the miR-204-3p/APC2 axis in oral squamous cell carcinoma. *Mol Carcinog*. 2019 Oct;58(10):1783-1794. doi: 10.1002/mc.23065.
  42. Li X, Wang C, Zhang H, Li Y, Hou D, Liu D, Xu R, Cheng J, Liu L, Fu Y, Ye J, Jiang H. circFNDC3B Accelerates Vasculature Formation and Metastasis in Oral Squamous Cell Carcinoma. *Cancer Res*. 2023 May 2;83(9):1459-1475. doi: 10.1158/0008-5472.CAN-22-2585.
  43. Tai Y, Li Y, Zhang M. Silencing of circ\_OSBP10 affects the functional behaviors of oral squamous cell carcinoma cells by the miR-299-3p/CDK6 axis. *Arch Oral Biol*. 2022 Apr;136:105363. doi: 10.1016/j.archoralbio.2022.105363.
  44. Xu S, Song Y, Shao Y, Zhou H. Hsa\_circ\_0060927 Is a Novel Tumor Biomarker by Sponging miR-195-5p in the Malignant Transformation of OLK to OSCC. *Front Oncol*. 2022 Jan 11;11:747086. doi: 10.3389/fonc.2021.747086.
  45. Guo L, Luo G, Liu Y, Xu J. Circular CDC like kinase 1 suppresses cell apoptosis through miR-18b-5p/Y-box protein 2 axis in oral squamous cell carcinoma. *Bioengineered*. 2022 Feb;13(2):4226-4234. doi: 10.1080/21655979.2022.2027174.
  46. Di Croce L, Helin K. Transcriptional regulation by Polycomb group proteins. *Nat Struct Mol Biol*. 2013 Oct;20(10):1147-55. doi: 10.1038/nsmb.2669.
  47. Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, Ghosh D, Pienta KJ, Sewalt RG, Otte AP, Rubin MA, Chinnaiyan AM. The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature*. 2002 Oct 10;419(6907):624-9.
  48. Bachmann IM, Halvorsen OJ, Collett K, Stefansson IM, Straume O, Haukaas SA, Salvesen HB, Otte AP, Akslen LA. EZH2 expression is associated with high proliferation rate and aggressive tumor subgroups in cutaneous melanoma and cancers of the endometrium, prostate, and breast. *J Clin Oncol*. 2006 Jan 10;24(2):268-73. doi: 10.1200/JCO.2005.01.5180.
  49. Kleer CG, Cao Q, Varambally S, Shen R, Ota I, Tomlins SA, Ghosh D, Sewalt RG, Otte AP, Hayes DF, Sabel MS, Livant D, Weiss SJ, Rubin MA, Chinnaiyan AM. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proc Natl Acad Sci U S A*. 2003 Sep 30;100(20):11606-11. doi: 10.1073/pnas.1933744100.
  50. Wu Y, Zhang L, Zhang L, Wang Y, Li H, Ren X, Wei F, Yu W, Liu T, Wang X, Zhou X, Yu J, Hao X. Long non-coding RNA HO-TAIR promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in oral squamous cell carcinoma. *Int J Oncol*. 2015;46(6):2586-94. doi: 10.3892/ijo.2015.2976.
  51. Xu J, Lin Q, Zhao X. Circular RNA 0000311 Aggravates the Aggressiveness of Oral Squamous Cell Carcinoma via miR-876-5p/EZH2 Axis. *J Environ Pathol Toxicol Oncol*. 2023;42(3):43-52. doi: 10.1615/JEnvironPatholToxicolOncol.2022041989.
  52. Yu Q, Du Y, Wang S, Zheng X. LncRNA PART1 promotes cell proliferation and inhibits apoptosis of oral squamous cell carcinoma by blocking EZH2 degradation. *J Biochem*. 2021 Sep 7;169(6):721-730. doi: 10.1093/jb/mvab026.
  53. Chen Y, Li Z, Liang J, Liu J, Hao J, Wan Q, Liu J, Luo C, Lu Z. CircRNA has\_circ\_0069313 induced OSCC immunity escape by miR-325-3p-Foxp3 axes in both OSCC cells and Treg cells. *Aging (Albany NY)*. 2022 May 16;14(10):4376-4389. doi: 10.18632/aging.204068.
  54. Yang Z, Chen W, Wang Y, Qin M, Ji Y. CircKRT1 drives tumor progression and immune evasion in oral squamous cell carcinoma by sponging miR-495-3p to regulate PDL1 expression. *Cell Biol Int*. 2021 Jul;45(7):1423-1435. doi: 10.1002/cbin.11581.
  55. Ju H, Wei D, Wu Y, Liu Y, Ding Q, Rui M, Fan Z, Yao Y, Hu J, Ren G. A pilot study of camrelizumab with docetaxel and cisplatin for the first line treatment in recurrent/metastatic oral squamous cell carcinoma. *MedComm (2020)*. 2023 Jul 22;4(4):e312. doi: 10.1002/mco.2.312.
  56. Zheng Y, Pan D. The Hippo Signaling Pathway in Development and Disease. *Dev Cell*. 2019 Aug 5;50(3):264-282. doi: 10.1016/j.devcel.2019.06.003.
  57. Totaro A, Panciera T, Piccolo S. YAP/TAZ upstream signals and downstream responses. *Nat Cell Biol*. 2018 Aug;20(8):888-899. doi: 10.1038/s41556-018-0142-z.
  58. Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, Elvassore

- N, Piccolo S. Role of YAP/TAZ in mechanotransduction. *Nature*. 2011 Jun 8;474(7350):179-83. doi: 10.1038/nature10137.
59. Zanconato F, Forcato M, Battilana G, Azzolin L, Quaranta E, Bodega B, Rosato A, Bicciato S, Cordenonsi M, Piccolo S. Genome-wide association between YAP/TAZ/TEAD and AP-1 at enhancers drives oncogenic growth. *Nat Cell Biol*. 2015 Sep;17(9):1218-27. doi: 10.1038/ncb3216.
60. Dong C, Wei KJ, Zhang WB, Sun H, Pan HY, Zhang L. LATS2 induced by TNF-alpha and inhibited cell proliferation and invasion by phosphorylating YAP in oral squamous cell carcinoma. *J Oral Pathol Med*. 2015 Jul;44(6):475-81. doi: 10.1111/jop.12317.
61. Peng QS, Cheng YN, Zhang WB, Fan H, Mao QH, Xu P. circRNA\_0000140 suppresses oral squamous cell carcinoma growth and metastasis by targeting miR-31 to inhibit Hippo signaling pathway. *Cell Death Dis*. 2020 Feb 10;11(2):112. doi: 10.1038/s41419-020-2273-y.
62. Schmierer B, Hill CS. TGFbeta-SMAD signal transduction: molecular specificity and functional flexibility. *Nat Rev Mol Cell Biol*. 2007 Dec;8(12):970-82. doi: 10.1038/nrm2297.
63. Blobe GC, Schiemann WP, Lodish HF. Role of transforming growth factor beta in human disease. *N Engl J Med*. 2000 May 4;342(18):1350-8. doi: 10.1056/NEJM200005043421807.
64. Massagué J. TGFbeta in Cancer. *Cell*. 2008 Jul 25;134(2):215-30. doi: 10.1016/j.cell.2008.07.001.
65. Wrana JL, Attisano L, Wieser R, Ventura F, Massagué J. Mechanism of activation of the TGF-beta receptor. *Nature*. 1994 Aug 4;370(6488):341-7. doi: 10.1038/370341a0.
66. Adylova A, Mukhanbetzhanovna AA, Attar R, Yulaevna IM, Farooqi AA. Regulation of TGFβ/SMAD signaling by long non-coding RNAs in different cancers: Dark Knight in the Castle of molecular oncology. *Noncoding RNA Res*. 2021 Jan 7;6(1):23-28. doi: 10.1016/j.ncrna.2020.12.003.
67. Zhao W, Cui Y, Liu L, Qi X, Liu J, Ma S, Hu X, Zhang Z, Wang Y, Li H, Wang Z, Liu Z, Wu J. Splicing factor derived circular RNA circUHRF1 accelerates oral squamous cell carcinoma tumorigenesis via feedback loop. *Cell Death Differ*. 2020 Mar;27(3):919-933. doi: 10.1038/s41418-019-0423-5.
68. Zhang X, Guo GY, Liu RY, Wu T, Wang ZH, Zhang ZT. CircLDLRAD3 inhibits Oral squamous cell carcinoma progression by regulating miR-558/Smad4/TGF-β. *J Cell Mol Med*. 2023 Aug 10. doi: 10.1111/jcmm.17898.
69. Yan J, Xu H. Regulation of transforming growth factor-beta1 by circANKS1B/miR-515-5p affects the metastatic potential and cisplatin resistance in oral squamous cell carcinoma. *Bioengineered*. 2021 Dec;12(2):12420-12430. doi: 10.1080/21655979.2021.2005221.
70. Cui Y, Liu J, Liu L, Ma X, Gui Y, Liu H, Zhao W. m6A-modified circFOXK2 targets GLUT1 to accelerate oral squamous cell carcinoma aerobic glycolysis. *Cancer Gene Ther*. 2023 Jan;30(1):163-171. doi: 10.1038/s41417-022-00526-6.
71. Ai Y, Wu S, Zou C, Wei H. Circular RNA circFOXO3 regulates KDM2A by targeting miR-214 to promote tumor growth and metastasis in oral squamous cell carcinoma. *J Cell Mol Med*. 2022 Mar;26(6):1842-1852. doi: 10.1111/jcmm.16533.
72. Cheng T, Huang F, Zhang Y, Zhou Z. Knockdown of circGOLPH3 inhibits cell progression and glycolysis by targeting miR-145-5p/lysine demethylase 2A (KDM2A) axis in oral squamous cell carcinoma. *Head Neck*. 2023 Jan;45(1):225-236. doi: 10.1002/hed.27229.
73. Hou Y, Yu W, Wu G, Wang Z, Leng S, Dong M, Li N, Chen L. Carcinogenesis promotion in oral squamous cell carcinoma: KDM4A complex-mediated gene transcriptional suppression by LEF1. *Cell Death Dis*. 2023 Aug 8;14(8):510. doi: 10.1038/s41419-023-06024-3.
74. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. *Nat Rev Cancer*. 2020 Feb;20(2):74-88. doi: 10.1038/s41568-019-0216-7.
75. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov*. 2014 Feb;13(2):140-56. doi: 10.1038/nrd4204.
76. Engelman JA. Targeting PI3K signalling in cancer: opportunities, challenges and limitations. *Nat Rev Cancer*. 2009 Aug;9(8):550-62. doi: 10.1038/nrc2664.
77. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. *Nat Rev Clin Oncol*. 2013 Mar;10(3):143-53. doi: 10.1038/nrclinonc.2013.10.
78. Xu B, Guo M, Ma L, Farooqi AA, Wang L, Qiao G, Liu M, Zuo L, Ye H, Lin X, Cao S. Mer15, a novel polypeptide from Meretrix, inhibits proliferation and metastasis of human non-small cell lung cancer cells through regulating the PI3K/Akt/mTOR signaling pathway. *Neoplasma*. 2021 Nov;68(6):1181-1189. doi: 10.4149/neo\_2021\_210509N628.
79. Wang L, Cheng L, Ma L, Ahmad Farooqi A, Qiao G, Zhang Y, Ye H, Liu M, Huang J, Yang X, Lin X, Cao S. Alnustone inhibits the growth of hepatocellular carcinoma via ROS-mediated PI3K/Akt/mTOR/p70S6K axis. *Phytother Res*. 2022 Jan;36(1):525-542. doi: 10.1002/ptr.7337.
80. Yılmaz S, Doğanyigit Z, Oflamaz AO, Ateş Ş, Söylemez ESA, Nisari M, Farooqi AA. Determination of Rutin's antitumoral effect on EAC solid tumor by AgNOR count and PI3K/AKT/mTOR signaling pathway. *Med Oncol*. 2023 Mar 27;40(5):131. doi: 10.1007/s12032-023-01999-7.
81. Zhou J, Jin S. Circ\_0058063 Contributed to Oral Squamous Cell Carcinoma Development by Sponging miR-145 and Regulating PI3K/AKT Pathway. *Mol Biotechnol*. 2023 Mar 16. doi: 10.1007/s12033-023-00715-0.
82. Jiang W, Zhang C, Zhang X, Sun L, Li J, Zuo J. CircRNA HIPK3 promotes the progression of oral squamous cell carcinoma through upregulation of the NUPR1/PI3K/AKT pathway by sponging miR-637. *Ann Transl Med*. 2021 May;9(10):860. doi: 10.21037/atm-21-1908.
83. Wang J, Jiang C, Li N, Wang F, Xu Y, Shen Z, Yang L, Li Z, He C. The circEPST11/mir-942-5p/LTBP2 axis regulates the progression of OSCC in the background of OSF via EMT and the PI3K/Akt/mTOR pathway. *Cell Death Dis*. 2020 Aug 12;11(8):682. doi: 10.1038/s41419-020-02851-w.
84. Gao L, Dou ZC, Ren WH, Li SM, Liang X, Zhi KQ. CircCDR1as upregulates autophagy under hypoxia to promote tumor cell survival via AKT/ERK1/2/mTOR signaling pathways in oral squamous cell carcinomas. *Cell Death Dis*. 2019 Oct 3;10(10):745. doi: 10.1038/s41419-019-1971-9.
85. Su W, Wang Y, Wang F, Zhang B, Zhang H, Shen Y, Yang H. Circular RNA hsa\_circ\_0007059 indicates prognosis and influences malignant behavior via AKT/mTOR in oral squamous cell carcinoma. *J Cell Physiol*. 2019 Sep;234(9):15156-15166. doi: 10.1002/jcp.28156.