

Advancements in Oral Cancer Therapeutics Using Long Non-coding RNAs

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Oral squamous cell carcinoma (OSCC) remains a major global health burden with limited therapeutic success. Advances in transcriptomic profiling have identified long non-coding RNAs (lncRNAs) as key regulators of OSCC progression and therapy resistance. This short communication summarizes recent developments in lncRNA-based therapeutic strategies identified through focused literature analysis using PubMed, Google Scholar, and ClinicalTrials.gov. Preclinical evidence from xenograft and patient-derived xenograft models demonstrates the potential of antisense oligonucleotides, RNA interference, CRISPR-based genome modulation, and exosome-mediated delivery to silence oncogenic lncRNAs or restore tumor-suppressive lncRNAs. Although clinical translation remains early, these findings highlight emerging precision therapeutic opportunities in OSCC.

Keywords: Antisense Oligonucleotide (ASO); Long Non-Coding RNAs (lncRNAs); Oral Squamous Cell Carcinoma (OSCC); RNA interference (RNAi); Therapeutics.

Oral squamous cell carcinoma (OSCC) is the most common subtype of head and neck squamous cell carcinoma (HNSCC) and represents a significant global health challenge. According to the GLOBOCAN 2022 report, approximately 389,485 new cases of lip and oral cavity cancer are diagnosed each year, resulting in 188,230 deaths worldwide.¹ The burden is particularly high in developing regions. Major risk factors include tobacco use, alcohol consumption, betel quid chewing, viral infections, and inadequate oral hygiene.^{2,3} Despite therapeutic advances, including targeted agents and immune checkpoint inhibitors, the five-year survival rate for OSCC remains close to 50%, with metastatic disease associated with even poorer outcomes.^{2,3} Challenges such as late-

stage diagnosis, intratumoral heterogeneity, and resistance to therapy necessitate the development of novel, more effective treatment strategies.

Recent advances in omics technologies have facilitated the identification of molecular regulators critical to OSCC pathogenesis. Among these, long non-coding RNAs (lncRNAs), transcripts longer than 200 nucleotides that do not encode proteins, have emerged as key modulators of gene expression.³⁻⁵ Their high tissue specificity, stability, and regulatory versatility render them promising diagnostic biomarkers and therapeutic targets. Dysregulation of lncRNAs is commonly observed in OSCC, with distinct lncRNAs functioning either as oncogenes or tumor suppressors.³⁻⁵ Therapeutic approaches aim

to inhibit oncogenic lncRNAs or restore tumor-suppressive lncRNAs using advanced molecular tools. This short communication highlights lncRNA-mediated therapeutic applications in OSCC animal models, summarizes current therapeutic strategies and recent advances, discusses associated challenges, and outlines future perspectives, thereby providing readers with an updated overview of this rapidly evolving field.

Therapeutic strategies using lncRNAs are broadly categorized: (i) transcript-level silencing using antisense oligonucleotides (ASOs) or RNA interference (RNAi) approaches, (ii) genomic or transcriptional modulation using genome-editing tools, and (iii) intercellular delivery and tumor microenvironmental modulation using exosome-based systems. Importantly, these strategies not only suppress oncogenic lncRNAs but also directly address lncRNA-mediated therapy resistance, a major barrier to effective OSCC management. By targeting lncRNAs involved in drug efflux, DNA damage repair, epithelial-mesenchymal transition, autophagy, and cancer stemness, these approaches collectively aim to restore therapeutic sensitivity and enhance treatment efficacy.

ASO-Based Targeting: ASOs represent one of the most developed modalities for lncRNA targeting. ASOs are short, synthetic nucleotide sequences designed to hybridize selectively with target lncRNAs, leading to transcript degradation or functional inhibition.⁶ Chemical modifications such as locked nucleic acid (LNA) incorporation enhance ASO stability and specificity while reducing off-target effects.⁷ Several ASO drugs have achieved clinical approval from FDA or EMA for various indications, demonstrating translational feasibility.⁸ In head and neck cancers, overexpression of lncRNAs like AC104041.1, ZEB1-AS1 and ZEB2-AS1 correlates with poor prognosis.^{7,9,10} Targeted silencing of these lncRNAs using ASOs or LNA-ASOs or nanoparticle-mediated delivery of ASOs/siRNAs has shown significant tumor-suppressive effects in vitro and in patient-derived xenograft (PDX) models, underscoring their therapeutic potential.^{7,9,10}

RNAi Mediated Silencing Strategies: These strategies, including siRNA and shRNA, constitute another potent approach for cytoplasmic lncRNA knockdown. Delivery vehicles such as lipid nanoparticles, liposomes, micelles, and

exosomes improve RNA molecule stability and tumor-specific uptake. Preclinical studies demonstrate effective suppression of oncogenic lncRNAs like LINC00460, ELDR, and PCAT1 with siRNA-mediated knockdown, resulting in inhibited tumor growth in xenograft models without systemic toxicity.¹¹⁻¹³

Among RNAi modalities, shRNA-mediated knockdown is the most widely used approach for in vivo functional validation of lncRNAs. For example, shRNA mediated silencing of KCNQ1OT1 restores cisplatin sensitivity, highlighting RNAi's potential to overcome chemoresistance in OSCC.¹⁴ Multiple other oncogenic lncRNAs have been validated in OSCC using shRNA-based knockdown. HOXA10-AS, LINC01929, SLC7A11-AS1, MIR4713HG, LINC01296, and CCAT1 are overexpressed in oral cancer tissues and cell lines, and their silencing significantly reduces tumor growth, tumor burden, and/or lung metastasis in xenograft models through diverse mechanisms, including miRNA sponging and protein stabilization.¹⁵⁻²⁰

Restoration of tumor suppressor lncRNAs via overexpression has also been evaluated. For example, MEG3, CASC2 and NKILA overexpression in xenograft models significantly reduced tumor volume and growth rates, highlighting the translational relevance of gene restoration strategies for therapeutic intervention.²¹⁻²³

Genome Editing and Transcriptional Modulation: Genome editing technologies, especially CRISPR/Cas systems, provide a versatile platform for precise lncRNA locus modulation. CRISPR-dCas9-mediated silencing of oncogenic lncRNAs such as PANDAR has demonstrated inhibition of proliferation and induction of apoptosis in OSCC cell lines.²⁴ Furthermore, Tao et al. demonstrated that CRISPR/Cas9-mediated genomic deletion of XIST significantly reduced tumor formation in tongue squamous cell carcinoma xenografts in nude mice.²⁵ Similarly, Chang et al. reported that CRISPR/Cas9 targeting of MIR31HG markedly attenuated OSCC oncogenicity, highlighting its therapeutic potential.²⁶ While obstacles related to off-target activity and efficient delivery persist, genome editing approaches hold promise for durable and specific tumor control. Alternative

methods like TALENs and zinc finger nucleases (ZFNs) have shown feasibility for lncRNA targeting in other malignancies, supporting their potential applicability in OSCC.²⁷

Exosome-Mediated Approaches: Exosomal lncRNAs have emerged as important mediators of intercellular communication within the tumor microenvironment. Exosomes, extracellular vesicles secreted by tumor and stromal cells, carry lncRNAs that modulate tumor progression and therapeutic resistance.⁴ Notable examples include cancer-associated fibroblast-derived FLJ22447 and macrophage-derived LBX1-AS1, both implicated in OSCC pathobiology.⁴ Engineering exosomes to deliver tumor-suppressive lncRNAs or siRNAs targeting oncogenic lncRNAs represents a promising, minimally invasive therapeutic strategy. Exosome-mediated overexpression of lncRNA PART1 reduced OSCC cell viability, migration, and invasion while enhancing apoptosis.²⁸ HOTTIP was found to be upregulated in M1 macrophage-

derived exosomes.²⁹ In Balb/c nude mice, HNSCC tumors treated with M1 macrophage-derived exosomes showed reduced growth, smaller tumor volumes, and increased apoptosis.²⁹

Implications in therapy resistance: Beyond their direct roles in tumor growth and metastasis, accumulating evidence indicates that dysregulated lncRNAs critically contribute to therapeutic resistance in OSCC, thereby limiting the efficacy of conventional treatments. Multiple lncRNAs implicated in mechanisms such as enhanced drug efflux, DNA damage repair, epithelial-mesenchymal transition, anti-apoptotic signaling, and cancer stem cell maintenance.³⁰ For instance, HOXA11-AS and UCA1 contribute to cisplatin resistance in OSCC by promoting proliferation and reducing apoptosis.³⁰ ANRIL enhances drug efflux via MRP1 and ABCC2 transporters, while HOTAIR facilitates resistance by inducing autophagy through ATG3/7 upregulation.³⁰ Targeting these lncRNAs could sensitize tumors

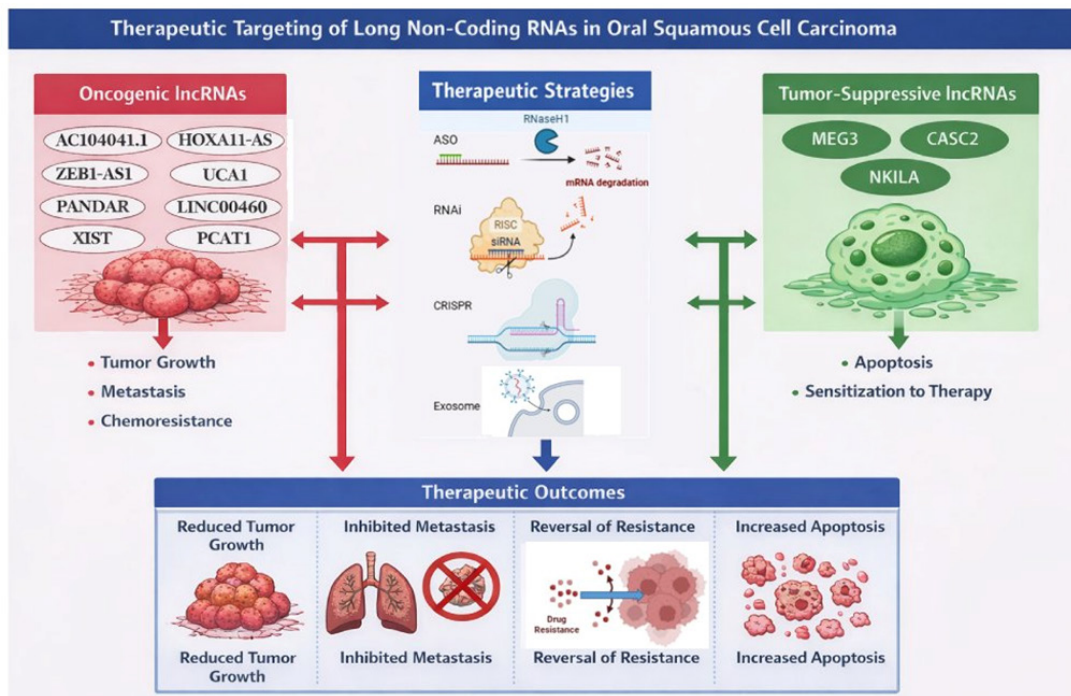


Fig. 1. Schematic representation of lncRNA-based therapeutic targeting in oral squamous cell carcinoma, highlighting oncogenic lncRNAs that drive tumor growth, metastasis, and chemoresistance, and tumor-suppressive lncRNAs that promote apoptosis and therapy sensitization. The central panel illustrates major therapeutic strategies, including antisense oligonucleotides, RNAi, CRISPR/Cas-based approaches, and exosome-mediated delivery, leading to reduced tumor growth, inhibited metastasis, reversal of resistance, and enhanced apoptosis. (Created using BioRender.com)

Table 1. Representative table of lncRNAs targeted in OSCC with therapeutic approaches and outcomes

lncRNA Name	Functional Classification	Therapeutic Modality	Measurable Outcomes
AC104041.1	Oncogenic	ASO (LNA-modified)	Reduces cell viability, migration; decreased tumor growth in PDX models ⁷
ZEB1-AS1	Oncogenic	ASO (nanoparticle delivery)	Tumor growth inhibition; overcoming cisplatin resistance ⁹
ZEB2-AS1	Oncogenic	ASO	ZEB2-AS1 knockdown significantly reduced tumor volume and weight relative to controls ¹⁰
LINC00460	Oncogenic	Cholesterol-conjugated siRNA	Intra tumor injection reduced xenograft tumor growth ¹¹
ELDR	Oncogenic	siRNA	Intra tumor injection reduced oral cancer PDX tumor growth ¹²
PCAT1	Oncogenic	siRNA	Intra tumor injection inhibited xenograft tumor growth ¹³
ANRIL	Oncogenic	siRNA	Decreased cell proliferation; enhanced apoptosis and cisplatin sensitivity ³⁰
HOXA11-AS	Oncogenic	shRNA	Decreased proliferation; increased apoptosis in resistant tumor growth ³⁰
UCA1	Oncogenic	shRNA	Reduced tumor growth and cisplatin sensitivity ³⁰
KCNQ1OT1	Cisplatin resistant	shRNA	KCNQ1OT1 depletion inhibits TSCC tumor growth and chemo-resistance in vivo ¹⁴
HOXA10-AS	Oncogenic	shRNA	Significantly reduces of in-vivo tumor growth ¹⁵
LINC01929	Oncogenic	shRNA	Reduces tumor growth and tumor weight ¹⁶
SLC7A11-AS1	Oncogenic	shRNA	Reduces tumor growth and lung metastasis ¹⁷
MIR4713HG	Oncogenic	shRNA	Reduces tumor growth and lung metastasis ¹⁸
LINC01296	Oncogenic	shRNA	Significantly reduces xenograft tumor growth ¹⁹
CCAT1	Oncogenic	shRNA	Significantly reduces xenograft tumor growth ²⁰
MEG3	Tumor suppressor	Overexpression	Reduced tumor size and growth in xenografts ²¹
CASC2	Tumor suppressor	Overexpression	Inhibited tumor growth in xenograft models ²²
NKILA	Tumor suppressive	shRNA	Over expression reduces tumor growth and knocked down increases tumor growth ²³
PANDAR	Oncogenic	CRISPR-dCas9	Suppressed proliferation; induced apoptosis ²⁴
XIST	Oncogenic	CRISPR-dCas9	Reduces tumor formation in nude mice ²⁵
MIR31HG	Oncogenic	CRISPR-dCas9	Reduces the oncogenicity of OSCC ²⁶
PART1	Exosomal	Exosomal delivery	Reduced cell viability, migration, and invasion while enhancing apoptosis ²⁸
HOTTIP	M1 macrophage-derived exosomes	Exosomal delivery	Inhibited tumor growth and induced apoptosis in xenograft models ²⁹

to chemotherapy and improve patient outcomes.³⁰

Thus, advances in ASO-, RNAi-, CRISPR-, and exosome-based strategies highlight lncRNAs as versatile and actionable therapeutic targets in OSCC (Figure 1 and Table 1), providing a strong preclinical foundation for their future integration into precision oncology frameworks.

DISCUSSION

OSCC remains a highly aggressive malignancy with limited improvements in long-term survival, highlighting the need for innovative molecularly targeted therapeutic strategies. Across multiple preclinical models, targeting oncogenic lncRNAs using ASOs, RNAi, CRISPR-based genome modulation, and exosome-mediated delivery consistently resulted in significant reductions in tumor volume, tumor weight, metastatic potential, and therapy resistance. Notably, lncRNAs such as ZEB2-AS1, ZEB1-AS1, HOXA11-AS, LINC00460, ELDR, PCAT1 etc. demonstrated robust tumor-suppressive responses upon targeted inhibition, directly linking lncRNA dysregulation to aggressive clinicopathological features of OSCC. Conversely, restoration of tumor-suppressive lncRNAs, including MEG3, CASC2, and NKILA, further supports the therapeutic relevance of both silencing and replacement strategies.

Importantly, Table 1 highlights the versatility and complementarity of different lncRNA-targeting modalities. ASO-based approaches offer translational promise due to their clinical maturity, RNAi strategies enable efficient *in vivo* functional validation, and CRISPR-dCas9 platforms provide locus-specific and potentially durable repression of oncogenic lncRNAs. Moreover, exosome-based delivery systems address TME-mediated signaling and therapeutic resistance, thereby expanding the scope of lncRNA-directed interventions.

Despite significant preclinical progress, clinical translation of lncRNA-directed therapies remains limited. Although lncRNAs such as MALAT1, EGFR-AS1, and DQ786243 have been examined in clinical trials for diagnostic and prognostic value,³ no lncRNA-targeted therapeutics have yet been approved for clinical use in OSCC.

Moving toward clinical application requires rigorous validation, detailed toxicological evaluation, and development of optimized delivery systems to ensure specificity, bioavailability, and molecular stability. Additionally, combination therapies integrating lncRNA modulation with established treatment modalities warrant extensive clinical investigation to maximize therapeutic efficacy. To overcome these challenges, the integration of chemical modifications, ligand-directed targeting, and next-generation nanoparticle or engineered exosome delivery systems may substantially enhance molecular stability, tumor selectivity, and safety profiles. Furthermore, patient stratification based on lncRNA expression signatures and molecular subtypes may facilitate precision-guided treatment selection. Continued efforts in systematic validation, delivery optimization, and biomarker-driven clinical trial design will be pivotal to translating these experimental advances into clinically effective and safe therapeutic interventions.

CONCLUSION

In conclusion, accumulating preclinical evidence supports the pivotal role of lncRNAs in regulating OSCC progression and therapeutic resistance. Studies employing ASO-, RNAi-, CRISPR-based, and exosome-mediated approaches consistently demonstrate that targeted inhibition of oncogenic lncRNAs or restoration of tumor-suppressive lncRNAs leads to reduced tumor growth, enhanced apoptosis, and improved therapeutic sensitivity in experimental models. Although these findings are largely limited to preclinical settings, they provide a strong mechanistic and translational rationale for further development of lncRNA-directed therapies. Future efforts focusing on optimized delivery systems, safety evaluation, and biomarker-driven patient stratification will be essential to advance these strategies toward clinical application. Collectively, lncRNA-targeted interventions represent a promising, yet still evolving, avenue for improving therapeutic outcomes in OSCC.

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Conflict of interest

The author does not have any conflict of interest.

Data availability statement

This statement does not apply to this article.

Ethics statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed consent statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Not applicable.

Author contributions

The sole author was responsible for the conceptualization, methodology, data collection, analysis, writing, and final approval of the manuscript

REFERENCES

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229–63.
- Irani S. New insights into oral cancer–risk factors and prevention: A review of literature. *Int J Prev Med.* 2020;11:202.
- Sur S, Davray D, Basu S, et al. Novel insights on oral squamous cell carcinoma management using long non-coding RNAs. *Oncol Res.* 2024;32(10):1589–612.
- Tang J, Fang X, Chen J, et al. Long non-coding RNA (lncRNA) in oral squamous cell carcinoma: Biological function and clinical application. *Cancers (Basel).* 2021;13(23).
- Coan M, Haeffliger S, Ounzain S, et al. Targeting and engineering long non-coding RNAs for cancer therapy. *Nat Rev Genet.* 2024;25(8):578–95.
- Collotta D, Bertocchi I, Chiapello E, et al. Antisense oligonucleotides: A novel frontier in pharmacological strategy. *Front Pharmacol.* 2023;14:1304342.
- Li M, Ding X, Zhang Y, et al. Antisense oligonucleotides targeting lncRNA AC104041.1 induce antitumor activity through the Wnt2B/β-catenin pathway in head and neck squamous cell carcinoma. *Cell Death Dis.* 2020;11(8):672.
- Cakan E, Lara OD, Szymanowska A, et al. Therapeutic antisense oligonucleotides in oncology: From bench to bedside. *Cancers (Basel).* 2024;16(17).
- Yang H, Zhang Y, Tan Z, et al. Nucleus-targeted silencer nanopatform regulating ZEB1-AS1 in head and neck squamous cell carcinoma therapy. *Discov Nano.* 2024;19(1):192.
- Diao P, Ge H, Song Y, et al. Overexpression of ZEB2-AS1 promotes epithelial-to-mesenchymal transition and metastasis by stabilizing ZEB2 mRNA in head and neck squamous cell carcinoma. *J Cell Mol Med.* 2019;23(6):4269–80.
- Jiang Y, Cao W, Wu K, et al. LncRNA LINC00460 promotes epithelial-to-mesenchymal transition in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 nuclear translocation. *J Exp Clin Cancer Res.* 2019;38(1):365.
- Sur S, Nakanishi H, Steele R, et al. Long non-coding RNA ELDR enhances oral cancer growth by promoting ILF3–cyclin E1 signaling. *EMBO Rep.* 2020;21(12):e51042.
- Sur S, Nakanishi H, Steele R, et al. Depletion of PCAT-1 in head and neck cancer cells inhibits tumor growth and induces apoptosis by modulating c-Myc–AKT1–p38 MAPK signaling pathways. *BMC Cancer.* 2019;19(1):354.
- Zhang S, Ma H, Zhang D, et al. LncRNA KCNQ1OT1 regulates proliferation and cisplatin resistance in tongue cancer via miR-211-5p–mediated Ezrin/FAK/Src signaling. *Cell Death Dis.* 2018;9(7):742.
- Chen YT, Kan CH, Liu H, et al. Modular scaffolding by lncRNA HOXA10-AS promotes oral cancer progression. *Cell Death Dis.* 2022;13(7):629.
- Che H, Che Y, Zhang Z, et al. Long non-coding RNA LINC01929 accelerates progression of oral squamous cell carcinoma by targeting the miR-137-3p/FOXC1 axis. *Front Oncol.* 2021;11:657876.

17. Liu Z, Wang X, Liu L, et al. Long non-coding RNA SLC7A11 antisense RNA 1 promotes oral squamous cell carcinoma progression by regulating ubiquitination of K-homology type splicing regulatory protein. *Arch Oral Biol.* 2023; 154:105762.
18. Jia B, Zheng X, Qiu X, et al. Long non-coding RNA MIR4713HG aggravates malignant behaviors in oral tongue squamous cell carcinoma via binding with microRNA let-7c-5p. *Int J Mol Med.* 2021;47(5).
19. Zhang S, Wang X, Wang D. Long non-coding RNA LINC01296 promotes progression of oral squamous cell carcinoma through activation of the MAPK/ERK signaling pathway via the miR-485-5p/PAK4 axis. *Arch Med Sci.* 2022;18(3):786–99.
20. Li GH, Ma ZH, Wang X. Long non-coding RNA CCAT1 is a prognostic biomarker for oral squamous cell carcinoma progression via the miR-181a-mediated Wnt/ β -catenin signaling pathway. *Cell Cycle.* 2019;18(21):2902–13.
21. Lin L, Liu X, Lv B. Long non-coding RNA MEG3 promotes autophagy and apoptosis of nasopharyngeal carcinoma cells via PTEN upregulation by binding to microRNA-21. *J Cell Mol Med.* 2021;25(1):61–72.
22. Pan L, Chen H, Bai Y, et al. Long non-coding RNA CASC2 serves as a ceRNA of microRNA-21 to promote PDCD4 expression in oral squamous cell carcinoma. *Onco Targets Ther.* 2019; 12:3377–85.
23. Hu D, Zhong T, Dai Q. Long non-coding RNA NKILA reduces oral squamous cell carcinoma development through the NF- κ B signaling pathway. *Technol Cancer Res Treat.* 2020; 19:1533033820960747.
24. Jia T, Wang F, Qiao B, et al. Knockdown of lncRNA PANDAR by CRISPR-dCas9 decreases proliferation and increases apoptosis in oral squamous cell carcinoma. *Front Mol Biosci.* 2021; 8:653787.
25. Tao B, Wang D, Yang S, et al. Cucurbitacin B inhibits cell proliferation by regulating X-inactive specific transcript expression in tongue cancer. *Front Oncol.* 2021; 11:651648.
26. Chang KW, Hung WW, Chou CH, et al. LncRNA MIR31HG drives oncogenicity by inhibiting the limb-bud and heart development gene during oral carcinoma. *Int J Mol Sci.* 2021;22(16).
27. Chehelgerdi M, Chehelgerdi M, Khorramian-Ghahfarokhi M, et al. Comprehensive review of CRISPR-based gene editing: Mechanisms, challenges, and applications in cancer therapy. *Mol Cancer.* 2024;23(1):9.
28. Du Y, Shuai Y, Wang H, et al. Exosome-mediated long non-coding RNA PART1 suppresses malignant progression of oral squamous cell carcinoma via the miR-17-5p/SOCS6 axis. *Turk J Med Sci.* 2023;53(3):630–9.
29. Jiang H, Zhou L, Shen N, et al. M1 macrophage-derived exosomes and their key molecule lncRNA HOTTIP suppress head and neck squamous cell carcinoma progression by upregulating the TLR5/NF- κ B pathway. *Cell Death Dis.* 2022;13(2):183.
30. Meng X, Lou QY, Yang WY, et al. The role of non-coding RNAs in drug resistance of oral squamous cell carcinoma and therapeutic potential. *Cancer Commun (Lond).* 2021;41(10):981–1006.