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Expression and functional role of *LncRNA GSEC* in oral squamous cell carcinoma

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Objective: The current investigation seeks to elucidate the regulatory impact of the long non-coding RNA GSEC *(lncRNA GSEC)* on oncogenic mechanisms in oral squamous cell carcinoma. **Methods:** The expression dynamics of GSEC were systematically mapped across in vitro systems, including healthy oral keratinocyte controls (NHOK) and their malignant counterparts (SCC-25, SCC-9, CAL-27), utilizing standardized qRT-PCR protocols. CAL-27 (highest *GSEC* expression) underwent siRNA-mediated knockdown. The assessment of cellular functions such as proliferation, apoptosis regulation, mobility, and invasion was conducted utilizing validated protocols: CCK-8 for cell viability assessment, flow cytometry for apoptotic cell identification, Transwell systems for measuring invasive ability, and scratch assay for migration analysis. mRNA and protein levels of proliferation/apoptosis markers (*Ki67*, *PCNA*, *BCL-2*, *BAX*, *caspase-9*) were analyzed by qRT-PCR, Western blot, and immunofluorescence. **Results:** *GSEC* was significantly upregulated in OSCC cells vs. NHOK ($p<0.05$), peaking in CAL-27 ($p<0.05$ vs. SCC-9/SCC-25). Downregulation of GSEC inhibited the proliferation, migration, and invasive capabilities of OSCC cells and promoted apoptosis with statistical significance ($p<0.05$). A decrease in *Ki67* and *PCNA* expression, accompanied by an increase in *BAX* and *caspase-9* and a decrease in *BCL-2* levels, was detected at the mRNA and protein levels, with all reaching statistical significance at the $p<0.05$ threshold. **Conclusions:** *GSEC* overexpression promotes OSCC malignancy by driving proliferation and inhibiting apoptosis. Targeting *GSEC* may offer diagnostic and therapeutic potential for OSCC.

Keywords: Proliferatio, Apoptosis, OSCC, *LncRNA GSEC*

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90% of all oral malignancies.[1] Global epidemiological data indicate that OSCC results in more than 500,000 new cases and 140,000 deaths annually, maintaining consistently high incidence and mortality rates.[2] Originating primarily from the oral mucosal epithelium, this tumor predominantly affects middle-aged and elderly males and is characterized by aggressive tissue infiltration, often involving adjacent

muscles, nerves, vascular systems, and the jawbone, with early lymph node metastasis being a common feature.[3-5] Etiologically, the progression of OSCC involves the synergistic action of multiple risk factors, including chronic irritation, tobacco/alcohol exposure, nutritional imbalance, viral infection, radiation, and genetic susceptibility, leading to complex pathological mechanisms that result in significant treatment challenges and poor prognosis.[2] In-depth studies have shown that the invasion and metastasis of OSCC are closely related to the aberrant activation of several classic oncogenic pathways (such as PI3K/AKT/mTOR, MAPK, Wnt/β-catenin, etc.) and the dysregulation of downstream effector molecules (like EMT-related transcription factors, cell cycle regulatory proteins, etc.), forming a complex regulatory network that drives the malignant phenotype of the tumor.[3] The current standard of care relies on surgical resection combined with radiotherapy and chemotherapy, while targeted and immunotherapy approaches remain in the exploratory phase without significant breakthroughs.[6] Despite continuous advancements in treatment modalities, the overall patient survival rate has not seen a significant improvement. Similar to other malignant tumors, the development and progression of OSCC involve a multi-gene, multi-factor regulatory network.[7,8] Therefore, elucidating the key molecular pathways is crucial for early identification, personalized treatment, and precise prognostic assessment.

Non-coding RNAs (ncRNAs) constitute over 98% of the human transcriptome. These are RNA molecules that do not encode proteins. Among them, long non-coding RNAs (*lncRNAs*) are defined as ncRNAs exceeding 200 nucleotides in length. LncRNAs are not translated into protein and exert their biological functions through mechanisms such as post-transcriptional regulation.[10-12] The *lncRNA GSEC* (also known as *DCPS-AS1 or ST3GAL4-AS1*) possesses a specific G-quadruplex (G4) structure, which is maintained by four guanine bases linked through Hoogsteen hydrogen bonds and classified as a non-canonical nucleic acid conformation.[13] Research indicates that G-quadruplex structures (G4S) are widely involved in biological processes, including transcription, polyadenylation, splicing, RNA metabolism, and stability regulation.[14] Recent studies have revealed the oncogenic role of lncRNA GSEC in various cancers, such as colorectal cancer, osteosarcoma, lung adenocarcinoma, hepatocellular carcinoma, and breast cancer, where it promotes tumor progression by modulating proliferation, migration, invasion, remodeling of the immune microenvironment, and epithelial-mesenchymal transition (EMT).[15-17] Its mechanism of action involves complex molecular networks; some studies suggest it acts as a competing endogenous RNA (ceRNA), sequestering microRNAs (miRNAs) to derepress the inhibition of downstream oncogenes, thereby activating key signaling pathways like Wnt/β-catenin and PI3K/AKT; alternatively, its G4 structure can directly bind and regulate transcription factor activity, influencing the expression levels of EMT-related molecules.[18-20]However, the expression level and mechanistic role of lncRNA GSEC in OSCC remain unclear. This study aims to delineate its functional significance in the pathogenesis of OSCC, providing a theoretical basis for discovering novel diagnostic and therapeutic targets.

Material and Methods

Cell Culture

Human oral keratinocytes that are normal (NHOK) along with OSCC cell lines—specifically SCC-25, CAL-27, and SCC-9—were sourced from Procell. The culturing of these cells was conducted in Dulbecco's Modified Eagle Medium (DMEM) enhanced with 10% fetal bovine serum (FBS—Gibco), while maintaining a constant temperature of 37°C and a CO_2 environment of 5%.

Plasmid Transfection

Construction of plasmids was facilitated by Hanbio Biotechnology Co., Ltd., located in Shanghai.Sufficient siRNA pooled against GSEC targets as well as control siRNA were sourced from Hongxun Biotechnology Co., Ltd., based in Suzhou. The transfection procedure employed Lipofectamine™ 2000 from Thermo Fisher Scientific, adhering strictly to the provided guidelines for use. The sequence designs are listed in Table 1.

Table 1. Sequence Design Details for *LncRNA GSEC*

si-GSEC-1	sense: 5' GGAGGUCACAACAGUACAA 3'
	antisense: 5'UUGUACUGUUGUGACCUCC3'
si-GSEC-2	sense: 5'GAUUCCUUGUGAAGAUAAU 3'
	antisense: 5' AUUATCUUCACAAGGAAUC 3'

qRT-PCR

RNA was purified from samples employing the TriQuick Reagent from Solarbio, Beijing. The synthesis of complementary DNA (cDNA) was accomplished utilizing the SureScript™ First-Strand cDNA Synthesis Kit obtained from GeneCopeia in the USA. qRT-PCR was performed utilizing a 2×SYBR Green qPCR Master Mix supplied by Servicebio in Wuhan, employing β-actin as the internal reference gene. The relative quantification of gene expression was determined employing the 2^−ΔΔCt methodology. Specific information regarding the primer sequences can be found in Table 2.

Table 2. Primer Design

GSEC-Fwd:	5' AGCAGGCTTGGGATGGTGT 3'
GSEC-Rev:	5' GGTTTAGGTGAGCAGGGTGG 3'
BCL2-F	5' AGGATTGTGGCCTTCTTTGA 3'
BCL2-R	5' GCACCTACCCAGCCTCCGTTAT 3'
Bax-F	5' CGCTGACGGCAACTTCAACTG 3'
Bax-R	5' ATGAGCACTCCCGCCACAAA 3'
CASPASE9-F	5' CGAACTAACAGGCAAGCAGC 3'
CASPASE9-R	5' ACATCACCAAATCCTCCAGAAC 3'
Ki67-F	5' AAGAAGAGGTCCTACCAGTCG 3'
Ki67-R	5' ATCCCAGTTCCATAGTTTGC 3'
PCNA-F	5' TCCAGGGCTCCATCCTCAAGA 3'
PCNA-R	5' CATATACGTGCAAATTCACCAGA 3'
β-actin-F	5' CGTGACATTAAGGAGAAGCTG 3'
β-actin-R	5' TAGAAGCATTTGCGGTGGAC 3'

Western Blotting

Overall protein was isolated by employing RIPA lysis buffer provided by Beyotime. The proteins were subjected to 10% SDS-PAGE separation and then blotted onto PVDF membranes. The membranes were then immersed in a solution of primary antibodies for a duration of 24 hours at 4°C: anti-*Caspase9* (1:1000 dilution, A18676, Sanying), anti-*BCL2* (1:1000 dilution, 12789-1-AP, Sanying), anti-*BAX* (1:1000 dilution, 50599-2-Ig, Sanying), and anti-*β-actin* (1:10,000 dilution, ab8227, Abcam). Following exposure to HRP-conjugated secondary antibodies at a dilution of 1:8000, the presence of protein bands was made apparent using an ECL detection kit from Wanleibio, and their cognate signals were quantified via chemiluminescence-based imaging techniques.

CCK-8 Assay

To assess cell proliferation, the CCK-8 assay, sourced from Beyotime in Shanghai, was utilized. One thousand cells per well were seeded into 96-well plates. At intervals of 24, 48, and 72 hours post-seeding, 10μL of CCK-8 reagent was added and the plates were incubated for 1 hour. Thereafter, absorbance measurements were conducted at 450 nm using a microplate reader.

Flow Cytometry

Following a 48-hour period post-transfection, the cells were collected, rinsed using phosphate-buffered saline (PBS), and then marked with Annexin V-FITC/PI (supplied by Beyotime) for a 15-minute interval in dark conditions. Subsequently, the measurement of apoptotic cell levels was carried out utilizing flow cytometric analysis (by BD Biosciences).

Transwell Assay

A population of 300,000 cells per milliliter was inoculated into Transwell inserts lined with Matrigel (pore size of 8 μm,

supplied by Thermo Fisher Scientific) utilizing a medium devoid of serum. The lower compartment's medium was made up of a 20% concentration of fetal bovine serum (FBS). Following a 48-hour incubation period, the cells that had migrated were treated with a 4% solution of paraformaldehyde for fixation, subsequently dyed using a 0.1% solution of crystal violet, and their numbers were determined using a microscope at a magnification of 100 times.

Wound Healing Assay

Fully confluent cell cultures were gently induced to form a wound using a sterile pipette tip.Upon rinsing with PBS, the cells were then grown in a medium devoid of serum.Photographs of the wound healing process were taken at intervals of 0, 24, and 48 hours post-initiation, and the closure was thereafter analyzed with the aid of the ImageJ software.

Immunofluorescence

The cells were treated with a 4% solution of paraformaldehyde for fixation, followed by a permeabilization step using 0.2% Triton X-100. After blocking with a 5% BSA solution, they were exposed to either anti-*Ki67* (diluted 1:200) or anti-*PCNA* (diluted 1:200) antibodies, with the incubation proceeding overnight at a temperature of 4°C. Fluorescence micrographs were obtained following the application of Alexa Fluor-tagged secondary antibodies (diluted 1:200) along with DAPI for staining.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 10.0 software (GraphPad, San Diego, CA, USA). All experiments were conducted with three independent biological replicates (n=3). Comparisons between two groups were assessed using a two-tailed Student's t-test. Comparisons among three or more groups were analyzed using a One-way Analysis of Variance (ANOVA). If the ANOVA test result was significant, Tukey's post-hoc test was subsequently employed for all possible pairwise comparisons. A p-value<0.05 was considered statistically significant.

Results

Profiling *GSEC* Expression within OSCC Cell Lines

qRT-PCR analysis revealed significantly higher GSEC expression in OSCC cell lines (SCC-25, CAL-27, SCC-9) compared to NHOK ($p< 0.05$) (Fig. 1A). Among OSCC cells, CAL-27 exhibited the most pronounced *GSEC* upregulation ($p< 0.05$ vs. SCC-9/SCC-25) and was selected for subsequent experiments.

Knockdown Efficiency of si-*GSEC*

Transfection with si-*GSEC*-1 and si-*GSEC*-2 in CAL-27 cells demonstrated significant GSEC suppression via qRT-PCR ($p<$ 0.05, Fig. 1C). si-*GSEC*-1 showed superior knockdown efficiency and was utilized for further investigations.

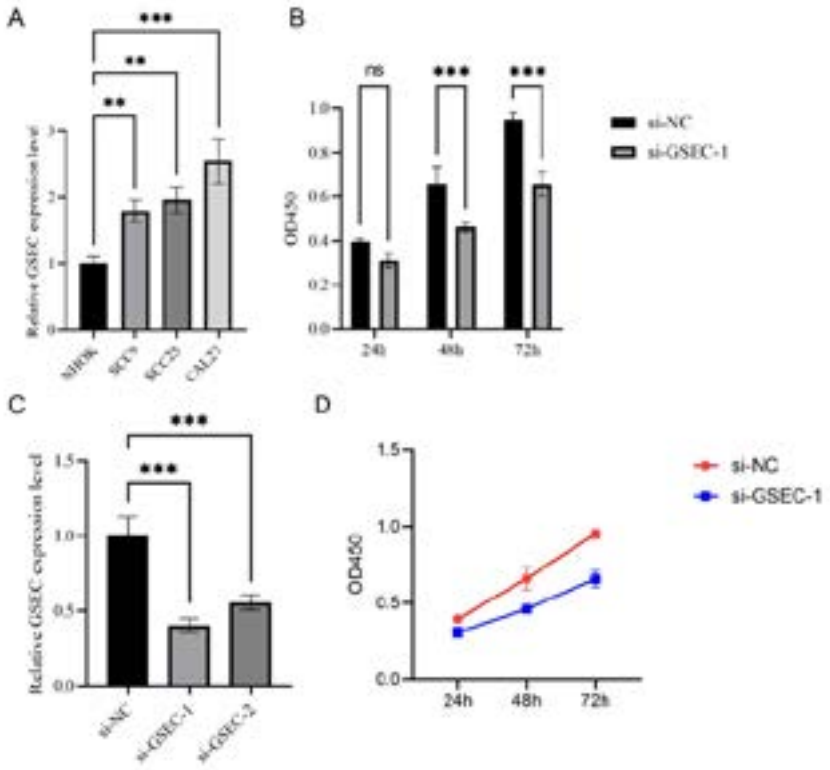
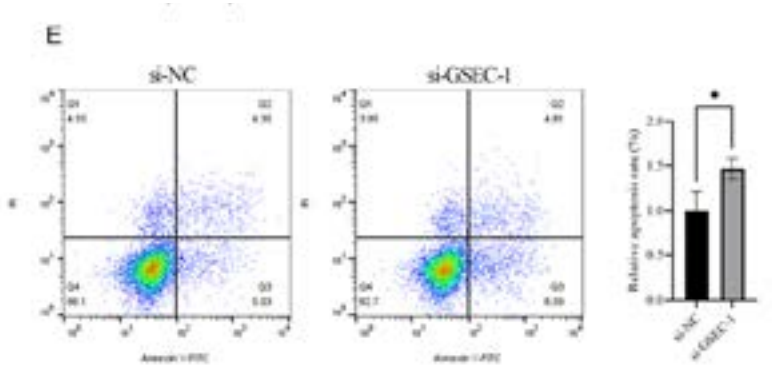


Figure 1A. The expression of GSEC in NHOK and OSCC cell lines
Figure 1B. The results of CCK8 cell proliferation assay
Figure 1C. si-GSEC transfection efficiency
Figure 1D. The results of CCK8 cell proliferation assay line graph
Figure 1E. CCK8 flow cytometry results
Statistical significance is denoted by asterisks: *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001



Functional Impact of *GSEC* on OSCC Cells

GSEC Promotes Proliferation and Suppresses Apoptosis

The CCK-8 assay results demonstrated that si-*GSEC* significantly inhibited cell proliferation in the CAL27 cell line compared to si-NC ($p< 0.05$, Fig. 1B). A noticeable inhibition of CAL27 cell proliferation was observed at the 24 h, 48 h, and 72 h incubation time points, with the most pronounced and statistically significant difference observed at the 72 h time point ($p< 0.05$, Fig. 1D).

Flow cytometry analysis revealed that si-*GSEC* significantly promoted apoptosis in CAL27 cells compared to the control group. Cells were allowed to reach approximately 60% confluence after 24 hours and were then transfected according to their respective groups. Cells were collected 48 hours post-transfection for the apoptosis assay, which showed that si-*GSEC* exerted a significant pro-early apoptotic effect ($p< 0.05$, Fig. 1E).

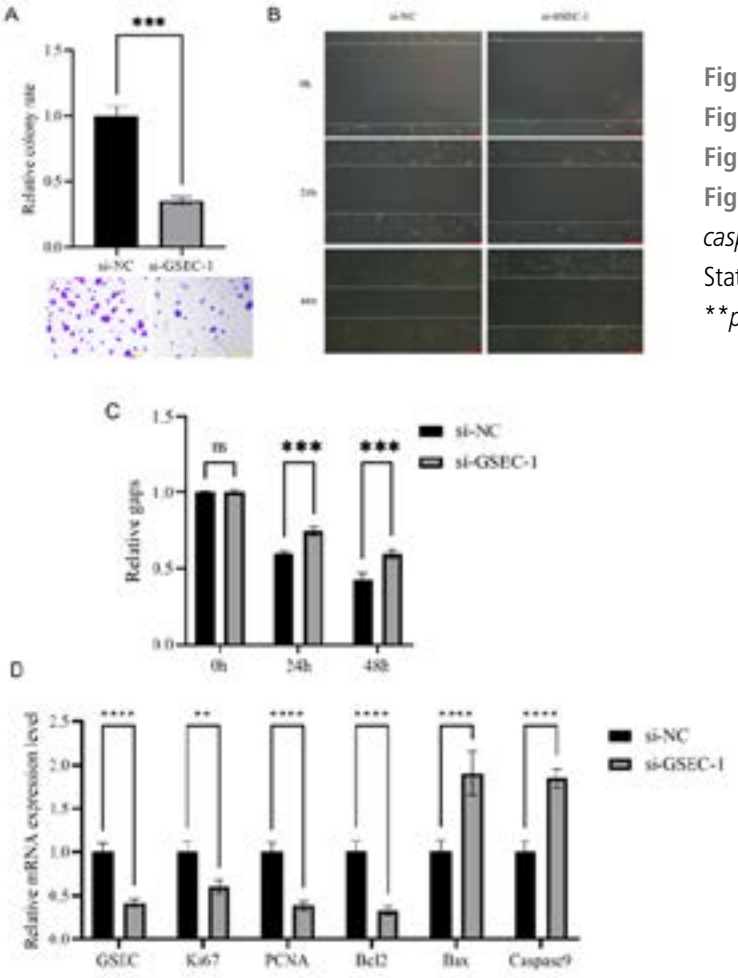


Figure 2A. Transwell experimental results
Figure 2B. Wound Healing Assay Results
Figure 2C. Bar Graph of Wound Healing Assay Results
Figure 2D. qRT-PCR detection of *GSEC*, *ki67*, *pcna*, *BCL-2*, *BAX*, *caspase-9*
Statistical significance is denoted by asterisks: **p*<0.05, ***p*<0.01, ****p*<0.001 and *****p*<0.0001

GSEC Enhances Invasion and Migration

The Transwell assay results showed that si-*GSEC* effectively inhibited the invasion capability of CAL27 cells compared to si-NC ($p< 0.05$). After 48 hours of incubation, the number of cells that invaded through the Matrigel matrix in the si-*GSEC* group was significantly reduced ($p<0.05$, Fig.2A). This finding suggests that *GSEC* can significantly promote the invasion capability of CAL27 cells.

The Wound Healing assay results indicated that the percentage of wound closure distance in the si-*GSEC* group was significantly lower than that in the si-NC group. Consequently, the cell migration rate in the si-*GSEC* group was lower than that in the si-NC group at both 24h and 48h time points ($p< 0.05$, Fig. 2B, C). This result suggests that *GSEC* can significantly enhance the migration capability of CAL27 cells.

mRNA Regulation of Proliferation/Apoptosis Markers

The qRT-PCR results confirmed successful cell transfection. Compared to the si-NC group, the expression levels of the apoptosis-related marker proteins *BAX* and caspase-9 were significantly upregulated in the si-*GSEC* group, while the expression of BCL-2 was clearly inhibited. Furthermore, the proliferation-related markers *Ki67* and *PCNA* showed significantly lower expression. All observed differences were statistically significant ($p < 0.05$). These findings further validate that *GSEC* influences biological behaviors such as proliferation and apoptosis in OSCC cells at the mRNA level (Fig.2D).

Protein-Level Validation

Western blot analysis was performed to detect three proteins: Bax, Bcl-2, and Caspase-9. Compared to the control group, the expression levels of the apoptosis-related markers Bax and Caspase-9 were significantly upregulated in the si-GSEC group, while the expression of Bcl-2 was clearly suppressed. These differences were statistically significant ($p<0.05$, Fig. 3A-D). These findings, at the protein level, demonstrate that GSEC exerts an inhibitory effect on apoptosis in OSCC cells. Immunofluorescence (IF) staining was used to detect the two proliferation-related proteins, Ki67 and PCNA. The results indicated that the expression of both proliferation markers, Ki67 and PCNA, was significantly lower in the si-GSEC group compared to the control group ($p< 0.05$, Fig. 3E, F). These protein-level results confirm that GSEC promotes tumor growth.

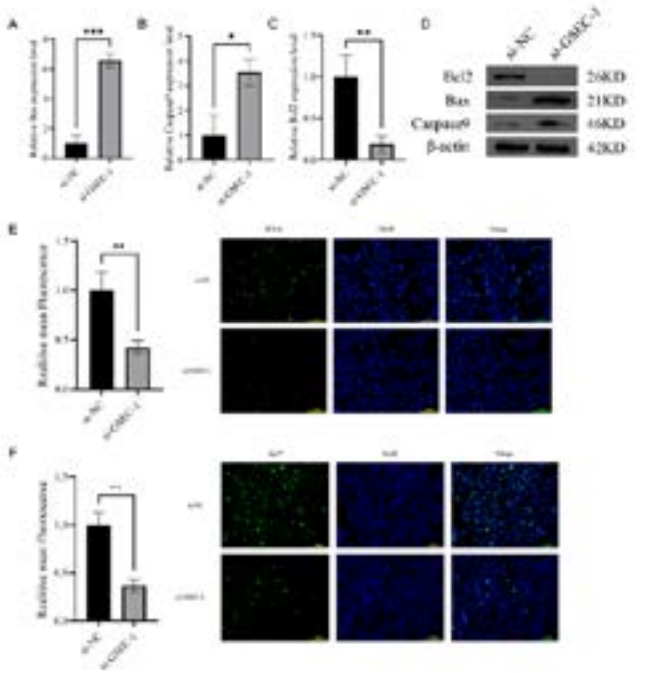


Figure 3A. Western blot detection of Bax results
Figure 3B. Western blot detection of caspase-9 results
Figure 3C. Western blot detection of Bcl-2 results
Figure 3D. Western blot detection of Bax, Bcl-2 and caspase-9 results
Figure 3E, F The results of *ki67* and *PCNA* were detected by immunofluorescence assay.
Statistical significance is denoted by asterisks: *$p<0.05$, **$p<0.01$, ***$p<0.001$, and ****$p<0.0001$.

Discussion

In this study, we first demonstrated that LncRNA *GSEC* is significantly overexpressed in oral squamous cell carcinoma (OSCC) cell lines and plays a crucial oncogenic role. The class of LncRNAs are increasingly recognized as key factors within oncogenesis, attracting increased attention towards unraveling their complex molecular functions.[21] Notably, *GSEC* exhibits significant overexpression in OSCC cell lines. Genetic intervention experiments demonstrated that *GSEC* silencing markedly suppresses tumor cell proliferation, invasion, migration, and induces apoptosis. Functionally, *GSEC* has the potential to facilitate tumorigenic properties through the regulation of the epithelial-mesenchymal transition process and proteins associated with the cell cycle.[18] Supporting this, Yang, et al.[19]

identified *GSEC* within an 18-LncRNA prognostic signature for lung adenocarcinoma (LUAD), with enriched pathways including EMT, hypoxia, stemness, and proliferation. Similarly, Fan et al.[20] revealed that *LncRNA LETS1* promotes TGFβ-induced EMT via TβR1 stabilization. These findings collectively highlight LncRNAs' roles in tumor progression through EMT regulation. This research elucidates the role of *GSEC* in regulating OSCC and highlights its potential as a therapeutic target for RNA-based interventions, which holds substantial promise for enhancing patient outcomes.

Multidimensional functional assays confirmed *GSEC*'s pivotal role in regulating OSCC malignant phenotypes. Gene silencing experiments demonstrated that *GSEC* knockdown significantly downregulated proliferation markers (*Ki67*, *PCNA*) while activating pro-apoptotic proteins (BAX, caspase-9) and suppressing anti-apoptotic BCL-2 ($p<0.05$). This molecular profile suggests *GSEC* orchestrates tumor proliferation through dual regulation of cell cycle progression (G1/S transition) and mitochondrial apoptosis.[22] Mechanistically, *GSEC* may interact with cyclin-dependent kinases (CDK4/6) to accelerate G1/S transition, paralleling the oncogenic function of DLEU2 reported by He, et al.[23], which promotes cell cycle progression via p53 suppression. Similarly, Fu, et al.[24] revealed that DICER1-AS1 regulates CDC5L nuclear translocation to block cell cycle in osteosarcoma. Notably, HOTAIR driven PI3K/AKT/mTOR activation in breast cancer[25] shares functional convergence with *GSEC*'s regulatory patterns, reinforcing the conserved role of LncRNAs in tumor proliferation networks.

Transwell invasion and wound healing assays demonstrated that *GSEC* suppression significantly impaired OSCC cell migration and invasion ($p< 0.05$). Mechanistically, tumor metastasis involves dynamic EMT regulation (evidenced by E-cadherin downregulation and N-cadherin upregulation), MMP-2/MMP-9 overexpression, and cytoskeletal reorganization (F-actin redistribution).[26] Notably, *GSEC* knockdown reduced pseudopodia formation and disrupted motility polarity, suggesting Rho GTPase (RhoA/ROCK) or integrin-mediated focal adhesion signaling involvement.[27] Supporting this, Zhou, et al.[28] identified LINC00460 mediated MMP-9 regulation via miR-539 sponging in thyroid cancer. Our findings align with Zhao et al.[29] who reported NEAT1's suppression of RhoA/ROCK through miR-490-3p in LUAD. These convergent mechanisms highlight *GSEC*'s role in coordinating metastatic cascades, positioning it as a multi-pathway therapeutic target.

Current standard therapies for OSCC remain confined to surgical resection combined with chemoradiotherapy, yet five-year survival rates stagnate at 50%-60% due to tumor heterogeneity and therapeutic resistance.[30,31] While EGFR-targeted therapies show partial efficacy, their clinical benefits are constrained by spatiotemporal heterogeneity and acquired resistance. Notably, breakthroughs in RNA therapeutics—including locked nucleic acid (LNA)-modified antisense oligonucleotides (e.g., HOTAIR inhibitors) and lipid-encapsulated siRNA (e.g., Patisiran, approved for hereditary transthyretin amyloidosis)—have propelled LncRNA-targeted agents into clinical trials, offering novel precision strategies for OSCC.[32-34]

The systematic findings of this study establish *GSEC* as a potent oncogenic driver in OSCC. These data provide a strong rationale for developing *GSEC* as a potential diagnostic biomarker for early-stage detection and relapse prediction, and as a novel RNA interference-based therapeutic target to improve precision intervention strategies for OSCC patients.

This study has limitations: 1) *GSEC*'s functional validation was restricted to cell lines without clinical correlation between *GSEC* expression and patient prognosis; 2) While proliferative/apoptotic protein alterations were observed, the precise molecular mechanisms (e.g., upstream regulators or downstream effectors) require further elucidation through in vivo models and multi-omics approaches.

Conclusion

This study identifies *GSEC* as an oncogenic LncRNA overexpressed in OSCC, driving tumor progression via proliferation, apoptosis, and metastasis regulation. Its conserved role across malignancies suggests broad therapeutic potential. Future investigations should delineate *GSEC*'s mechanistic networks and develop RNA-based targeting strategies to advance precision oncology in OSCC.

Conflict of Interest

The authors declare that no competing interests exist. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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