Seminars in Medical Writing and Education. 2025; 4:708
doi: 10.56294/mw2025708

ORIGINAL

Expression and Prognostic Relevance of LncRNA GSEC in HNSC: Focus on OSCC

Expresión y relevancia pronóstica de LncRNA GSEC en HNSC: Focus on OSCC

Deleheibateer[1,2], Od Bayarsaikhan[3], Ganbayar Batmunkh[1], Xu Wu[4], Xingan Zhou[2], Shiirevnyamba Avirmed[1]

[1]Graduate school, Mongolian National University of Medical Sciences. Zorig street, Ulaanbaatar 14120, Mongolia.
[2]Department of Stomatology, Affiliated Hospital of Inner Mongolia Medical University. Hohhot, Inner Mongolia, 010000, China.
[3]Department of Orthodontics, School of Dentistry, Mongolian National University of Medical Sciences. Zorig street, Ulaanbaatar 14120, Mongolia.
[4]Oral and maxillofacial surgery department, Hohhot Stomatological Hospital. Hohhot, Inner Mongolia, 010000, China.

Cite as: Deleheibateer, Bayarsaikhan O, Batmunkh G, Wu X, Zhou X, Avirmed S. Expression and Prognostic Relevance of LncRNA GSEC in HNSC: Focus on OSCC. Seminars in Medical Writing and Education. 2025; 4:708. https://doi.org/10.56294/mw2025708

Submitted: 27-01-2025 **Revised:** 04-03-2025 **Accepted:** 08-07-2025 **Published:** 09-07-2025

Editor: PhD. Prof. Estela Morales Peralta

Corresponding Author: Shiirevnyamba Avirmed

ABSTRACT

Introduction: in recent years, the role played by long noncoding RNAs (lncRNAs) in the development and progression of cancer has gained considerable interest. This study sought to identify diagnostic and prognostic lncRNAs in head and neck squamous cell carcinoma (HNSC) through bioinformatic analysis. Based on preliminary analyses and research objectives, lncRNA GSEC was selected for further investigation of its expression in HNSC and validation in oral squamous cell carcinoma (OSCC) tissues.
Method: transcriptomic data from RNA sequencing and patient data for HNSC were obtained from the Cancer Genome Atlas (TCGA) database. Differentially expressed lncRNAs were detected, and univariate Cox regression was used to identify prognostic lncRNAs. The random forest algorithm ranked the importance of differentially expressed lncRNAs, and the top 30 lncRNAs were intersected with Cox regression results to select diagnostic biomarkers. UCSC XENA provided TCGA and GTEx RNA-seq data in TPM format. Xiantao Academic was used in the pan-cancer analysis to evaluate GSEC expression in cancers. UALCAN and Kaplan-Meier (K-M) analyzed GSEC expression, clinical correlations, and prognostic value in HNSC. Immune cell infiltration was evaluated using Xiantao Academic. GSEC co-expressed genes in HNSC (FDR < 0,05, top 200) underwent GO/KEGG enrichment analysis using Metascape. Tissue samples were collected from CCEO and qRT-PCR was performed to validate GSEC expression and its association with clinical parameters.
Results: a total of 2385 lncRNAs showed differential expression in HNSC (1598 upregulated, 787 downregulated). Cox univariate analysis identified 1306 lncRNAs linked to HNSC outcomes (P < 0,05). The intersection of the top 30 lncRNAs from the random forest ranking and the Cox regression results identified LINC02156, AL353807.5, and GSEC (Alias: lncRNA ST3GAL4-AS1) as diagnostic biomarkers. GSEC was selected for pan-cancer analysis and was found to be differentially expressed in various tumors and significantly upregulated in HNSC (P < 0,05). There was a correlation with pathological stage, clinical grade, and immune cell infiltration in HNSC (P < 0,05), but no correlation with age and sex (P > 0,05). High GSEC expression predicted an adverse prognosis (P < 0,05). Co-expression gene enrichment analysis highlighted associations with GO terms such as “endoplasmic reticulum lumen” (GO:0005788) and “carbohydrate derivative biosynthesis” (GO:1901177), and KEGG pathways including “glucosaminoglycan biosynthesis” (hsa00532) and “nucleotide metabolism” (hsa01232). qRT-PCR validation confirmed GSEC overexpression in HNC tissues (P < 0,05), correlating with T stage and lymph node metastasis (P < 0,05), but not with age, sex, or differentiation grade (P > 0,05).
Conclusions: bioinformatic analyses revealed that GSEC is significantly upregulated in HNSC and is associated with diagnosis, prognosis, and immune infiltration, suggesting its potential as a therapeutic target. Validation in HNC tissues demonstrated its role in tumor progression, particularly related to T stage and lymph node

metastasis. These findings highlight GSEC as a pro-oncogenic factor in HNC pathogenesis, warranting further mechanistic exploration and providing a theoretical basis for GSEC-based precision therapy.

Keywords: HNSC; OSCC; lncRNA GSEC; Random Forest.

RESUMEN

Introducción: en los últimos años, el papel que juegan los ARN no codificantes de larga duración (lncRNAs) en el desarrollo y avance del cáncer ha ganado un interés considerable. Este estudio buscó identificar lncRNAs diagnósticos y pronósticos en el carcinoma de células escamosas de cabeza y cuello (HNSC) por medio del análisis bioinformático. Con base en los análisis preliminares y los objetivos de la investigación, se selección lncrna GSEC para una mayor investigación de su expresión en HNSC y su validación en tejidos de carcinoma de células escamosas oral (CCE).
Método: los datos transcriptómicos de la secuenciación del ARN y los datos de pacientes para HNSC se obtuvieron de la base de datos del Atlas del genoma del cáncer (TCGA). Se detectaron lncRNAs diferencialmente expresados y se utilizó la regresión univariable de Cox para identificar lncRNAs pronósticos. El algoritmo random Forest clasificó la importancia de los lncRNAs diferencialmente expresados, y los mejores 30 lncRNAs fueron intersecados con resultados de regresión de Cox para seleccionar biomarcadores de diagnóstico. UCSC XENA proporcionó datos TCGA y GTEx RNA-seq en formato TPM. Xiantao Academic se usó en el análisis pancancerpara evaluar la expresión de GSEC en los cánceres. UALCAN y Kaplan-Meier (K-M) analizaron la expresión de GSEC, las correlaciones clínicas y el valor pronóstico en el HNSC. Se evaluó la infiltrde células inmunmediante Xiantao Academic. Los genes coexpresados de GSEC en HNSC (FDR < 0,05, top 200) fueron sometidos a un análisis de enriquecimiento GO/KEGG usando Metascape. Se recogieron muestras de tejido de CCEO y se realizó qRT-PCR para validar la expresión de GSEC y su asociación con parámetros clínicos.
Resultados: un total de 2385 lncRNAs mostraron expresión diferencial en HNSC (1598 upregulated, 787 downregulated). El análisis univariado de Cox identificó 1306 lncRNAs vinculados a los resultados de HNSC (P < 0,05). La intersección de los 30 mejores lncRNAs de random Forest ranking y los resultados de la regresión de Cox identificaron LINC02156, AL353807.5, y GSEC(Alias:lncRNA ST3GAL4-AS1) como biomarcadores de diagnóstico. Se seleccionó GSEC para el análisis pancancery se encontró que el gen se expresaba diferencialmente en varios tumores y se regularon significativamente en HNSC (P < 0,05). Hubo una correlación con el estadio patológico, el grado clínico y la infiltrde células inmundel HNSC (P < 0,05), pero no hubo correlación con la edad y el sexo (P > 0,05). Una expresión alta de GSEC predijo un pronóstico adverso (P < 0,05). El análisis de enriquecimiento de genes co-expresados destacó asociaciones con términos de GO como “retículo endoplásmico lumen” (GO:0005788) y” biosíntesis de derivados de carbohidratos “(GO:1901177), y vías KEGG incluyendo” biosíntesis de glucosaminoglicanos “(hsa00532) y” metabolismo de nucleótidos “(hsa01232). La validación qRT-PCR confirmó la sobreexpresión de GSEC en los tejidos del CCEO (P < 0,05), correlacionándose con el estadio T y la metástasis en los ganglios linfáticos (P < 0,05), pero no con la edad, el sexo o el grado de diferenciación (P > 0,05).
Conclusiones: los análisis bioinformáticos revelaron que GSEC está significativamente regulada en HNSC y se asocia con diagnóstico, pronóstico e infiltración inmune, lo que sugiere su potencial como diana terapéutica. La validación en los tejidos del CCEO demostró su papel en la progresión tumoral, particularmente relacionado con el estadio T y la metástasis en los ganglios linfáticos. Estos hallazgos destacan GSEC como un factor pro-oncogénico en la patogénesis del CCEO, lo que justifica una mayor exploración mecaniy proporcionar una base teórica para la terapia de precisión basada en GSEC.

Palabras clave: HNSC; OSCC; lncRNA GSEC; Bosque Aleatorio.

INTRODUCTION

Head and neck cancer is among the most prevalent cancers worldwide. noting an annual incidence surpassing 900 000 cases, coupled with consistently elevated death rates.[1] Despite advancements in diagnostic and therapeutic strategies, the 5-year survival rate remains suboptimal due to tumor heterogeneity, frequent recurrence, and metastasis.[2,3] Oral squamous cell carcinoma (OSCC), comprising 30 % - 40 % of HNC cases, is the predominant subtype. Its pathogenesis is strongly associated with smoking, alcohol consumption, and HPV infection, characterized by aggressive invasiveness and poor prognosis.[4,5,6] The pressing challenges in clinical practice highlight the imperative to discover innovative molecular markers and treatment objectives for enhancing patient prognoses.

Over the last years, long non-coding RNAs (lncRNAs) have become significant controllers in the development

and advancement of neoplastic diseases.[7] These transcripts modulate diverse oncogenic processes, including proliferation, invasion, and metastasis, through epigenetic regulation, transcriptional interference, and post-transcriptional modifications.[8] Various lncRNAs have been associated with the advancement of OSCC. For instance, Niu et al.[9] demonstrated that HOXA11-AS promotes OSCC progression via the miR-98-5p/YBX2 axis, revealing a potential therapeutic target. Similarly, Lu et al.[10] identified LncOCMRL1 as a driver of OSCC growth and metastasis through the RRM2/EMT pathway. while Kim et al.[11] linked EIF3J-DT to chemoresistance in OSCC. The researchs underscores the varied functions that lncRNAs exert in the development of OSCC, along with their potential for countering the spread of disease and resistance to therapies.

Bioinformatics, an interdisciplinary field integrating systems biology and computational methodologies, provides powerful tools for deciphering complex molecular networks.[12] By synthesizing multi-omics data emerging domains like epigenomics and metabolomics[13,14,15] it enables systematic identification of disease-associated biomarkers. Advanced machine learning algorithms further enhance this process by prioritizing key regulatory factors through feature importance ranking,[16,17] offering unprecedented opportunities for precision oncology.

Building on these insights, this study employs TCGA database analysis combined with bioinformatics and machine learning approaches to identify critical lncRNAs in head and neck squamous cell carcinoma (HNSC), with a focus on OSCC. Through systematic validation, we aim to elucidate the biological functions and molecular mechanisms of candidate lncRNAs, thereby advancing our understanding of OSCC pathogenesis and identifying novel diagnostic and therapeutic targets.

METHOD

Data Acquisition and Analysis

Transcriptomic profiles and clinical metadata for 515 HNSC cases and 44 matched normal tissues were retrieved from TCGA (https://portal.gdc.cancer.gov).[18] The "edgeR" R package was utilized to carry out differential expression analysis for lncRNAs, setting the statistical significance criteria of $|\log_2 FC| > 1$, PValue <0,05. Univariate Cox regression analysis was conducted on differentially expressed lncRNAs in combination with clinical data.

Screening and Validation of Disease Signature Genes

A random forest model was constructed using the "randomForest" package.[19] The validity of the model was assessed using the ROC curve analysis. Mean Decrease in Accuracy and Mean Decrease in Gini were used to calculate the importance score of each lncRNA. The top 30 lncRNAs ranked by both methods were visualized. The intersection of these lncRNAs with those significantly associated with prognosis in the univariate Cox regression analysis was identified as critical candidates. The target lncRNA GSEC was selected for further analysis based on its biological relevance.

Pan-Cancer Analysis

The expression data of the target lncRNA were further analyzed. TPM-normalized RNA sequencing data from TCGA and GTEx, uniformly processed through the Toil pipeline, were downloaded from UCSC XENA (https://xenabrowser.net/datapages/).[20] Pan-cancer expression differences of the target lncRNA were analyzed by comparing tumor samples from TCGA with corresponding normal tissue data from GTEx. Visualization of the results was performed using Xiantao Academic (https://www.xiantaozi.com/).

Expression of Target lncRNA in HNSC and Correlation with Clinical Parameters

The Wilcoxon rank-sum test was employed to evaluate target lncRNA expression differences between tumor and normal tissues in TCGA/GTEx datasets. Data extraction and visualization were performed using the Xiantao Academic Platform(https://www.xiantaozi.com/). The dataset from the UALCAN platform (https://ualcan.path.uab.edu/)[21] was employed to investigate the varying expression patterns of the lncRNA in question and to evaluate its correlation with both clinical and pathological aspects. The assessment of prognostic significance was performed using the Kaplan-Meier Plotter platform (https://kmplot.com/analysis/).[22]

Immune Cell Infiltration Analysis of Target lncRNA in HNSC

To investigate immune infiltration characteristics, the Xiantao Academic Platform (https://www.xiantaozi.com/) was employed to correlate target lncRNA expression with immune cell infiltration levels. Immune cell proportions were calculated using a deconvolution algorithm embedded in the platform. Spearman correlation analysis was performed, and heatmaps were generated to visualize associations.

Functional Enrichment Analysis of Co-Expressed Genes

Co-expressed genes of the target lncRNA in HNSC were retrieved from cBioPortal for Cancer Genomics,[23]

an open-source platform integrating multi-omics data (e.g., TCGA, ICGC). Genes were selected based on FDR < 0,05 and ranked within the top 200 for further analysis. The functional categorization of GO and the pathway clustering of KEGG were performed employing Metascape,[24] followed by the visualization of the findings.

qRT-PCR Validation of Target lncRNA in OSCC Tissues

Tissue samples (~10 mg) were homogenized, followed by total RNA isolation using Solarbio's (Beijing) TriQuick Reagent according to manufacturer protocols. cDNA was generated with the SureScript™ First-Strand cDNA Synthesis Kit (GeneCopeia, US). qRT-PCR amplification employed Servicebio's (Wuhan) 2× SYBR Green kit, with ß-actin serving as the internal control. Relative expression was quantified via the 2−ΔΔCt method. Primer sequences are listed in table 1.

Table 1. Primer Sequences

ß-actin-F	5' CGTGACATTAAGGAGAAGCTG 3'
ß-actin-R	5' TAGAAGCATTTGCGGTGGAC 3'
GSEC-Fwd:	5' AGCAGGCTTGGGATGGTGT 3'
GSEC-Rev:	5' GGTTTAGGTGAGCAGGGTGG 3'

Correlation of Target lncRNA Expression with Clinical Parameters in OSCC Tissues

Encompassing a sample of 30 OSCC patients, this research was collected at the Affiliated Hospital of Inner Mongolia Medical University, with patient admissions spanning from the month of July 2024 to February 2025. All patients were pathologically confirmed with primary OSCC, without concurrent malignancies or prior radiotherapy/chemotherapy. A comprehensive dataset was compiled by collecting tumor and surrounding healthy tissues, coupled with the entirety of the patients' clinical histories. The Ethics Committee granted approval for the research protocol, with all subjects providing their informed consent. Target lncRNA expression in OSCC tissues was quantified by qRT-PCR and correlated with clinicopathological parameters.

Statistical Analysis

Data analysis was performed using R (v4.5.0) and RStudio,[25] with GraphPad Prism 10 for statistical visualization. Independent and paired t-tests were used for differential expression analysis. Non-parametric statistical analyses, including Spearman's rank correlation for ordinal data and Kruskal-Wallis alongside Mann-Whitney U tests for evaluating differences in variables across categories, were conducted. The threshold for statistical significance was $P < 0,05$, with FDR controlled via the Benjamini-Hochberg method.

RESULTS

Dataset Collection and Analysis

A total of 16882 lncRNAs were extracted from HNSC transcriptomic data. Employing the edgeR ($|\log_2 FC| > 1$, PValue <0,05) package, a total of 2385 lncRNAs with differential expression were detected, consisting of 1,598 that were upregulated and 787 that were downregulated, as depicted in the volcano plot shown in figure 1A. Univariate Cox regression analysis revealed 1306 lncRNAs significantly associated with HNSC prognosis.

Screening Results of Disease Signature Genes

A random forest model was applied to screen critical genes from the 2385 differentially expressed lncRNAs (figure 1B). The model's performance was evaluated by ROC curves (AUC = 0,995) (figure 1C). Top 30 lncRNAs were pinpointed utilizing a scoring system that derives feature importance from Mean Decrease in Accuracy and Mean Decrease in Gini, as illustrated in figure 1D. Intersection of these genes with univariate Cox regression results identified 12 candidates, among which LINC02156, AL353807.5, and GSEC exhibited diagnostic potential (figure 1E). Literature review highlighted GSEC's diagnostic and prognostic roles in multiple cancers but limited reports in HNSC, warranting further investigation.

Pan-Cancer Expression Profile of GSEC

Analysis of TCGA and GTEx datasets revealed differential expression of GSEC across multiple cancer types. Pan-cancer analysis revealed GSEC was upregulated in tumor tissues of BRCA, CHOL, ESCA, GBM, HNSC, LAML, LGG, PAAD, SKCM, STAD, and UCS, while downregulated in ACC, COAD, DLBC, KIRC, OV, PCPG, PRAD, READ, TGCT, THCA, and THYM. These findings suggest that GSEC may play context-dependent pro-tumorigenic or tumor-suppressive roles in different cancers (figure 2A).

GSEC Expression in HNSC and Correlation with Clinical Parameters

Wilcoxon test using TCGA and GTEx datasets confirmed significant GSEC upregulation in HNSC tumors (P < 0,05) (figure 2B, C). Analysis by UALCAN revealed significant relationships between GSEC expression levels and disease pathological stages (P < 0,05). However, no significant links were observed with respect to the patients' age or gender (P > 0,05)(figure 2D-H). Results from Kaplan-Meier estimation demonstrated a significant association between elevated GSEC levels and decreased OS, as evidenced by P values less than 0,05, while no significant relationship was found with PFS with P values exceeding 0,05, as depicted in figure 3A and B. ROC curve analysis yielded an AUC of 0,936 for GSEC in HNSC (figure 3C).

Immune Infiltration Profiling of GSEC in HNSC

GSEC expression showed positive associations with gamma delta T cells (Tgd), natural killer (NK) cells, and macrophage infiltration, while exhibiting negative correlations with CD8+ T cells, Th17 cells, and B cells (P<0,05). Results were visualized using a ggplot2-generated lollipop plot (figure 3D).

GO/KEGG Enrichment Analysis of GSEC in HNSC

Metascape analysis of the top 200 co-expressed genes identified enrichment in biological processes such as "endoplasmic reticulum lumen" (GO:0005788) and "carbohydrate derivative biosynthesis" (GO:1901177), and KEGG pathways including "glycosaminoglycan biosynthesis" (hsa00532) and "fluid shear stress and atherosclerosis" (hsa05418) (figure 3 E,F).

GSEC Expression in OSCC Tissues

qRT-PCR analysis revealed markedly elevated expression levels of GSEC in OSCC tissues as opposed to their respective non-cancerous nearby tissues, with statistical significance (P < 0,05, figure 4 A, B).

Correlation of GSEC Expression with Clinicopathological Parameters in OSCC

GSEC expression significantly differed between T1-2 and T3-4 TNM stages (P < 0,05) (table 1, figure 4C) and between lymph node metastasis groups (P < 0,05) (figure 4D). No associations were observed with age, sex, or High/low grade (P > 0,05) (figure 4 E-G).

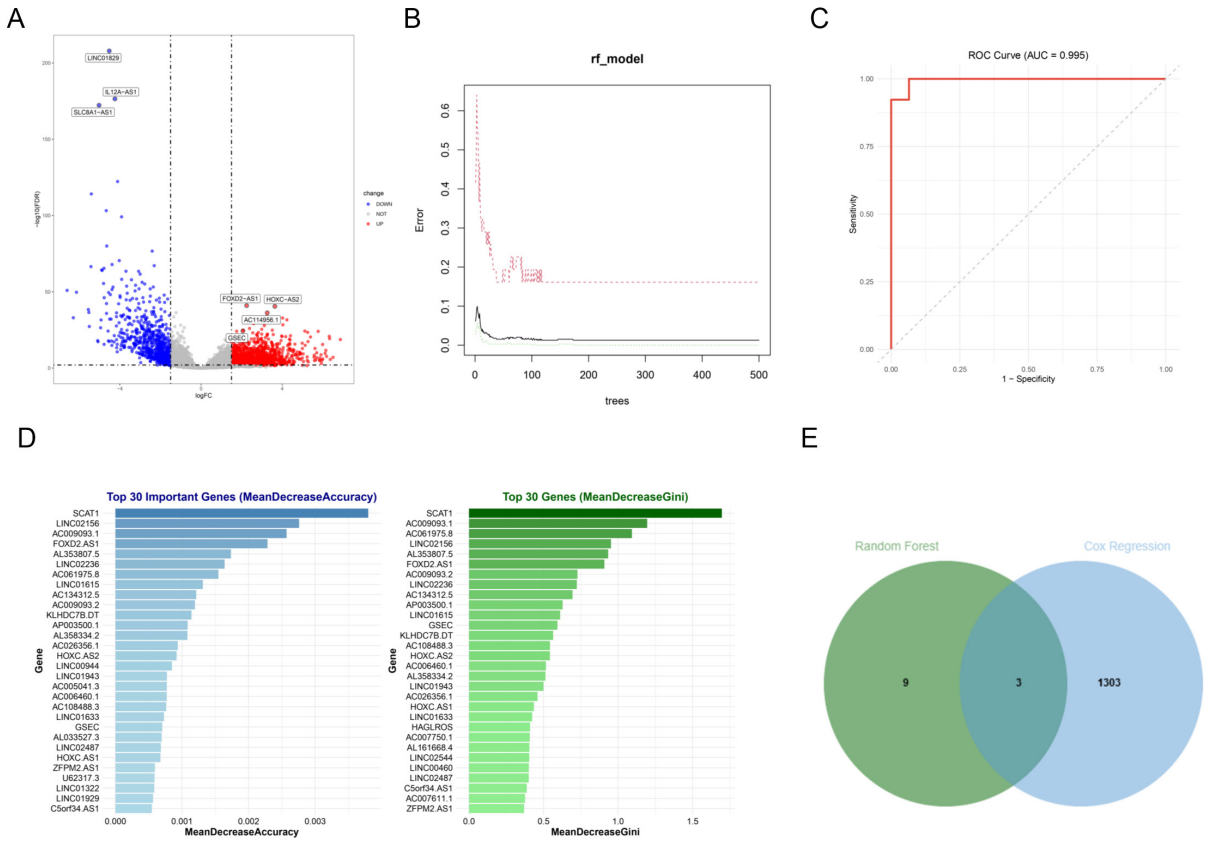

Figure 1. A. Volcano plot of differential lncRNA analysis in the TCGA database B. Random forest model; C. ROC curve of the random forest model; D. Top 30 genes ranked by importance in the random forest model; E. Overlap of 12 shared genes from two random forest algorithms and lncRNAs significant in Cox regression analysis

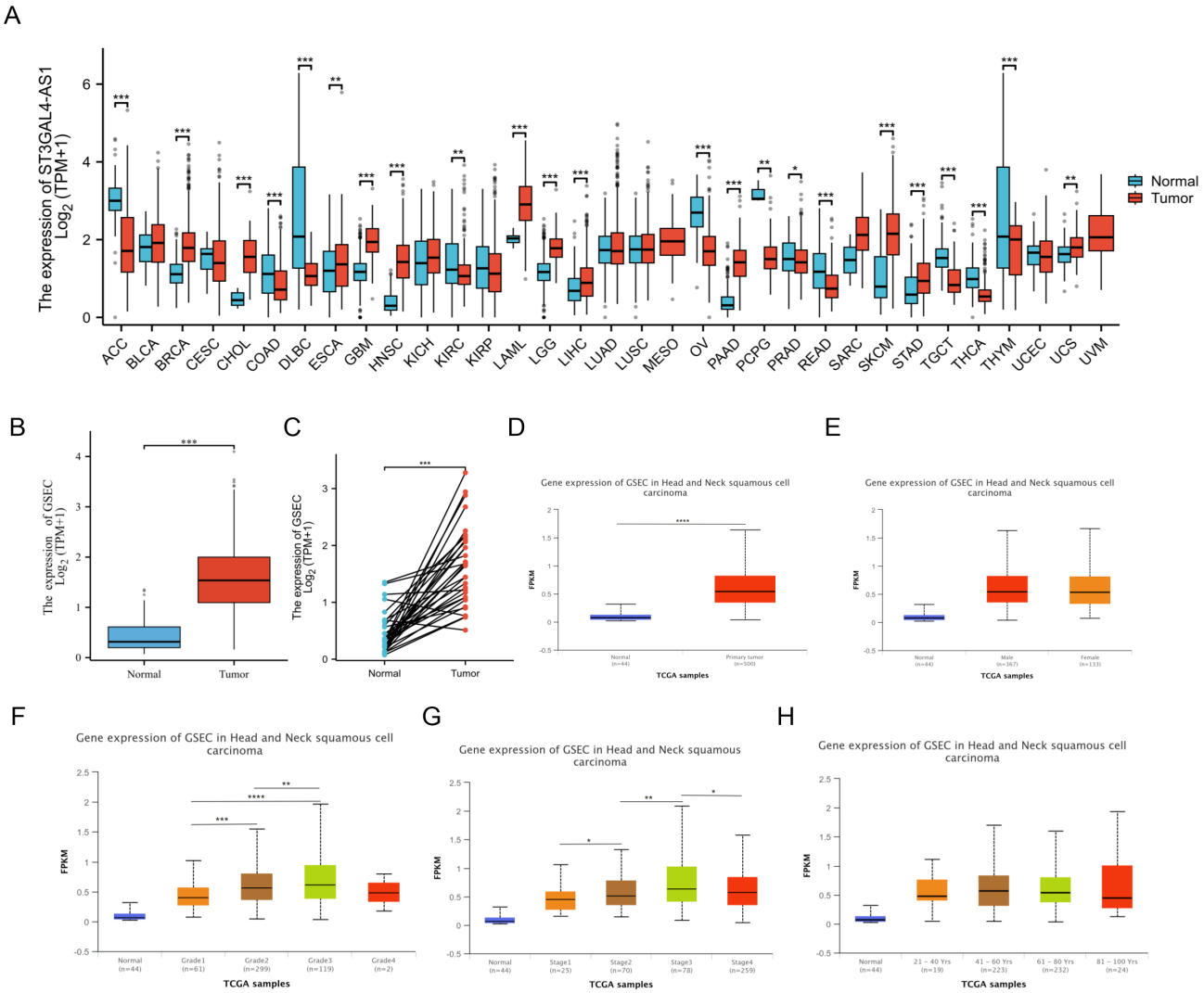

Figure 2. A. GSEC (ST3GAL4-AS1) expression across cancers in TCGA/GTEx cohorts (n=18,102). B. Xiantao Academic analysis of GSEC levels in HNSC. C. GSEC expression differences in matched HNSC tissues. D. UALCAN evaluation of GSEC expression variation. E. Gender-related GSEC expression patterns in HNSC. F. Tumor grade association with GSEC expression in HNSC. G. Pathological stage correlation with GSEC levels in HNSC. H. Age-dependent GSEC expression changes in HNSC patients. nsP>0,05, *P<0,05, **P<0,01, ***P<0,001, ****P<0,0001

Table 2. Association of LncRNA GSEC Expression with Clinical Parameters

Characteristics	Group	Total	High	Low	P Value
Gender	Male	19	9	10	0,9131
	Female	11	6	5	
Age	<60	17	9	8	0,6909
	≧60	13	6	7	
T stage	1/2	12	1	11	<0,001
	3/4	18	14	4	
Lymphatic metastasis or not	0	12	3	9	0,008
	1/3	18	12	6	
Pathological differentiation	L	16	9	7	0,9579
	H	14	6	8	

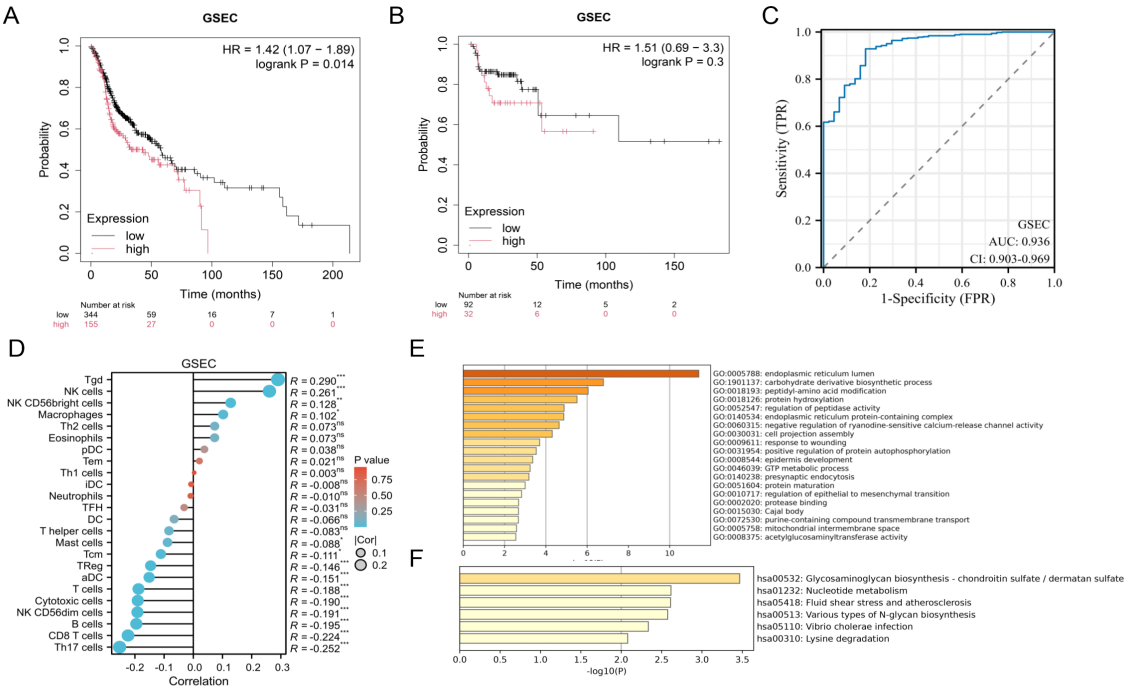

Figure 3. A. Correlation between GSEC expression and OS in HNSC. B. Correlation between GSEC expression and PFS in HNSC. C. ROC curve of GSEC in HNSC (AUC = 0,936). D. Immune infiltration patterns associated with GSEC expression in HNSC. E. Functional annotation of GSEC-interacting genes via GO analysis. F. KEGG-based pathway mapping of GSEC-correlated genes in HNSC

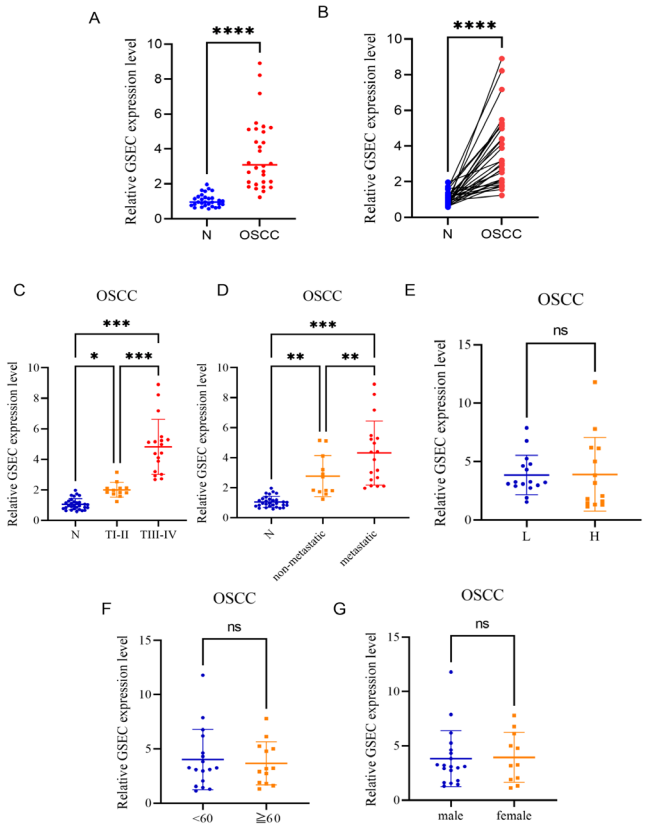

Figure 4. A. GSEC expression comparison in OSCC tumors vs. adjacent non-tumor tissues. B. Paired tumor-normal tissue GSEC levels in OSCC. C. Association of GSEC expression with T stage in OSCC. D. Lymph node metastasis correlation with GSEC levels in OSCC. E. Tumor differentiation grade (high/low) association with GSEC in OSCC. F. Age-related GSEC expression variations in OSCC. G. Association of GSEC expression with sex in OSCC.
nsP>0,05, *P<0,05, **P<0,01, ***P<0,001, ****P<0,0001

https://doi.org/10.56294/mw2025708 ISSN: 3008-8127

DISCUSSION

Head and neck cancer is among prevalent cancers globally, posing significant health burdens due to elevated incidence and mortality.[2,26] HNSC, the predominant subtype, exhibits significant molecular heterogeneity and complexity, and the mechanisms underlying its initiation and metastasis remain poorly understood. Thus, identifying novel clinical biomarkers and therapeutic targets to reduce recurrence and metastasis is critical for improving survival outcomes.[27] Recent studies have explored the roles of lncRNAs in HNSC, revealing regulatory networks involving lncRNAs, miRNAs, and mRNAs that may contribute to its pathogenesis.[28,29,30,31,32]

Our computational analysis of TCGA datasets was strategically employed to identify prognostic lncRNAs in HNSC, leveraging its comprehensive multi-omics profiles and clinical annotations for systematic biomarker discovery. This approach revealed GSEC as a critical lncRNA alongside LINC02156 and AL353807.5—a finding of particular significance given its established yet tissue-context-dependent oncogenic roles. While GSEC (alias ST3GAL4-AS1/DCPS-AS1) drives progression in hepatocellular carcinoma through miR-101-3p/SNX16/PAPOLG ceRNA networks modulating macrophage polarization,[33] promotes osteosarcoma metastasis via miR-588/EIF5A2 signaling,[34] and facilitates triple-negative breast cancer oncogenesis by sequestering miR-202-5p to activate AXL,[35] its mechanistic role in HNSC remained unexplored. Notably, in lung adenocarcinoma, GSEC regulates EGLN3 through miR-873-3p interactions[36] and correlates with methylation-driven pathways encompassing epithelial-mesenchymal transition, hypoxia, and disulfidptosis/ferroptosis.[37,38,39,40,41,42] Our study thus provides the first evidence implicating GSEC in HNSC pathogenesis, suggesting its function may transcend cancer types while exhibiting tissue-specific regulatory patterns. This divergence underscores the necessity of context-dependent lncRNA investigation and positions GSEC as a potential therapeutic target unique to HNSC microenvironments.

To elucidate the tissue oncogenic behavior of GSEC, we employed pan-cancer analysis. Our findings align with existing literature study results.[33,34,35,36,37,38,39,40,41,42,43,44] Crucially, we extends these observations by establishing GSEC's clinical relevance in HNSC. This specific divergence underscores GSEC's potential as a unique therapeutic target in HNSC microenvironments.

Immune infiltration analysis demonstrated that GSEC negatively correlates with CD8+ T cells, Th17 cells, and B cells, potentially suppressing adaptive immunity via extracellular matrix (ECM) remodeling (e.g.,glycosaminoglycan biosynthesis),[45] IL-6/STAT3 signaling dysregulation, or impaired tertiary lymphoid structure (TLS) formation.[46,47,48,49] Conversely, positive correlations with Tgd cells, NK cells, and macrophages suggest pro-tumor mechanisms, such as IL-17-driven angiogenesis.[50,51] NK cell exhaustion via HLA-E/NKG2A signaling, and M2 macrophage polarization.[52] These findings underscore GSEC's role in shaping an immunosuppressive tumor microenvironment (TME).

Functional enrichment analysis revealed GSEC's involvement in glycosaminoglycan biosynthesis (KEGG: hsa00532), nucleotide metabolism (hsa01232), and fluid shear stress pathways (hsa05418), supporting its role in ECM remodeling, metabolic reprogramming, and vascular adaptation. GO terms such as "endoplasmic reticulum lumen" (GO:0005788) and "carbohydrate derivative biosynthesis" (GO:1901177) further suggest GSEC's impact on protein secretion and post-translational modifications (e.g., phosphorylation, ubiquitination), potentially driving oncogenic signaling.[53,54]

QRT-PCR assessment verified the increased expression of GSEC in OSCC specimens, which correlated highly with the later stages of TNM classification and the occurrence of lymphatic metastases. No correlations were found with patient age, gender, or the level of tumor differentiation. The findings underscore the role of GSEC as a prospective marker both for diagnosing and treating OSCC.

CONCLUSIONS

This study identified GSEC as a key lncRNA in HNSC through bioinformatics analysis, validated its upregulation in HNSC tissues via qRT-PCR. These findings highlight GSEC's potential as a diagnostic marker and therapeutic candidate. Our multidisciplinary approach, combining bioinformatics and experimental validation, provides new insights into lncRNA-driven mechanisms in HNSC. Future studies should elucidate GSEC's functional roles in OSCC, particularly its regulation of critical signaling pathways or epigenetic modifications, to advance precision therapeutic strategies and improve patient outcomes.

BIBLIOGRAPHIC REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-49. doi:10.3322/caac.21660.

2. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020 Nov 26;6(1):92. doi:10.1038/s41572-020-00224-3.

3. Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. Med Sci (Basel). 2023 Jun 13;11(2):42. doi:10.3390/medsci11020042.

4. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, et al. Oral squamous cell carcinomas: state of the field and emerging directions. Int J Oral Sci. 2023 Sep 22;15(1):44. doi:10.1038/s41368-023-00249-w.

5. Bugshan A, Farooq I. Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. F1000Res. 2020 Apr 2;9:229. doi:10.12688/f1000research.22941.1.

6. Guo Z, Li K, Ren X, Wang X, Yang D, Ma S, et al. The role of the tumor microenvironment in HNSCC resistance and targeted therapy. Front Immunol. 2025 Apr 1;16:1554835. doi:10.3389/fimmu.2025.1554835.

7. Zhang Y. LncRNA-encoded peptides in cancer. J Hematol Oncol. 2024 Aug 12;17(1):66. doi:10.1186/s13045-024-01591-0.

8. Tan YT, Lin JF, Li T, Li JJ, Xu RH, Ju HQ. LncRNA-mediated posttranslational modifications and reprogramming of energy metabolism in cancer. Cancer Commun (Lond). 2021 Feb;41(2):109-20. doi:10.1002/cac2.12108.

9. Niu X, Yang B, Liu F, Fang Q. LncRNA HOXA11-AS promotes OSCC progression by sponging miR-98-5p to upregulate YBX2 expression. Biomed Pharmacother. 2020 Jan;121:109623. doi:10.1016/j.biopha.2019.109623.

10. Lu N, Jiang Q, Xu T, Gao Q, Wang Y, Huang Z, et al. LncOCMRL1 promotes oral squamous cell carcinoma growth and metastasis via the RRM2/EMT pathway. J Exp Clin Cancer Res. 2024 Sep 30;43(1):267. doi:10.1186/s13046-024-03190-w.

11. Kim SH, Kim HJ, Kim YJ, Kim YH, Park HR. LncRNA EIF3J-DT promotes chemoresistance in oral squamous cell carcinoma. Oral Dis. 2024 Nov;30(8):4909-20. doi:10.1111/odi.14987.

12. Anashkina AA, Leberfarb EY, Orlov YL. Recent Trends in Cancer Genomics and Bioinformatics Tools Development. Int J Mol Sci. 2021 Nov 10;22(22):12146. doi:10.3390/ijms222212146.

13. Sharma R, Kaur G, Bansal P, Chawla V, Gupta V. Bioinformatics Paradigms in Drug Discovery and Drug Development. Curr Top Med Chem. 2023;23(7):579-88. doi:10.2174/1568026623666221229113456.

14. Uesaka K, Oka H, Kato R, Kanie K, Kojima T, Tsugawa H, et al. Bioinformatics in bioscience and bioengineering: Recent advances, applications, and perspectives. J Biosci Bioeng. 2022 Nov;134(5):363-73. doi:10.1016/j.jbiosc.2022.08.004.

15. Gauthier J, Vincent AT, Charette SJ, Derome N. A brief history of bioinformatics. Brief Bioinform. 2019 Nov 27;20(6):1981-96. doi:10.1093/bib/bby063.

16. Chen C, Hou J, Tanner JJ, Cheng J. Bioinformatics Methods for Mass Spectrometry-Based Proteomics Data Analysis. Int J Mol Sci. 2020 Apr 20;21(8):2873. doi:10.3390/ijms21082873.

17. Chen Q, Meng X, Liao Q, Chen M. Versatile interactions and bioinformatics analysis of noncoding RNAs. Brief Bioinform. 2019 Sep 27;20(5):1781-94. doi:10.1093/bib/bby050.

18. Wang Z, Jensen MA, Zenklusen JC. A Practical Guide to The Cancer Genome Atlas (TCGA). Methods Mol Biol. 2016;1418:111-41. doi:10.1007/978-1-4939-3578-9_6.

19. Greener JG, Kandathil SM, Moffat L, Jones DT. A guide to machine learning for biologists. Nat Rev Mol Cell Biol. 2022 Jan;23(1):40-55. doi:10.1038/s41580-021-00407-0.

20. Wang S, Xiong Y, Zhao L, Gu K, Li Y, Zhao F, et al. UCSCXenaShiny: an R/CRAN package for interactive analysis of UCSC Xena data. Bioinformatics. 2022 Jan 3;38(2):527-9. doi:10.1093/bioinformatics/btab561.

21. Chandrashekar DS, Karthikeyan SK, Korla PK, Patel H, Shovon AR, Athar M, et al. UALCAN: An update to the integrated cancer data analysis platform. Neoplasia. 2022 Mar;25:18-27. doi:10.1016/j.neo.2022.01.001.

22. Győrffy B. Integrated analysis of public datasets for the discovery and validation of survival-associated genes in solid tumors. Innovation (Camb). 2024 Apr 9;5(3):100625. doi:10.1016/j.xinn.2024.100625.

23. de Bruijn I, Kundra R, Mastrogiacomo B, Tran TN, Sikina L, Mazor T, et al. Analysis and Visualization of Longitudinal Genomic and Clinical Data from the AACR Project GENIE Biopharma Collaborative in cBioPortal. Cancer Res. 2023 Dec 1;83(23):3861-7. doi:10.1158/0008-5472.CAN-23-0816.

24. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, et al. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. Nat Commun. 2019 Apr 3;10(1):1523. doi:10.1038/s41467-019-09234-6.

25. Giorgi FM, Ceraolo C, Mercatelli D. The R Language: An Engine for Bioinformatics and Data Science. Life (Basel). 2022 Apr 27;12(5):648. doi:10.3390/life12050648.

26. Bhat GR, Hyole RG, Li J. Head and neck cancer: Current challenges and future perspectives. Adv Cancer Res. 2021;152:67-102. doi:10.1016/bs.acr.2021.05.002.

27. Chen SMY, Krinsky AL, Woolaver RA, Wang X, Chen Z, Wang JH. Tumor immune microenvironment in head and neck cancers. Mol Carcinog. 2020 Jul;59(7):766-74. doi:10.1002/mc.23162.

28. Tian X, Hu D, Wang N, Zhang L, Wang X. LINC01614 is a promising diagnostic and prognostic marker in HNSC linked to the tumor microenvironment and oncogenic function. Front Genet. 2024 Apr 9;15:1337525. doi:10.3389/fgene.2024.1337525.

29. Ding Q, Lin F, Huang Z, Li Y, Cai S, Chen X, et al. Non-coding RNA-related FCGBP downregulation in head and neck squamous cell carcinoma: a novel biomarker for predicting paclitaxel resistance and immunosuppressive microenvironment. Sci Rep. 2024 Feb 23;14(1):4426. doi:10.1038/s41598-024-55210-6.

30. Rong M, Zhang M, Dong F, Wu K, Cai B, Niu J, et al. LncRNA RASAL2-AS1 promotes METTL14-mediated m6A methylation in the proliferation and progression of head and neck squamous cell carcinoma. Cancer Cell Int. 2024 Mar 25;24(1):113. doi:10.1186/s12935-024-03302-8.

31. Li Z, Qiu X, He Q, Fu X, Ji F, Tian X. CCND1-associated ceRNA network reveal the critical pathway of TPRG1-AS1-hsa-miR-363-3p-MYO1B as a prognostic marker for head and neck squamous cell carcinoma. Sci Rep. 2023 Jul 22;13(1):11831. doi:10.1038/s41598-023-38847-7.

32. Gao C, Lu W, Lou W, Wang L, Xu Q. Long noncoding RNA HOXC13-AS positively affects cell proliferation and invasion in nasopharyngeal carcinoma via modulating miR-383-3p/HMGA2 axis. J Cell Physiol. 2019 Aug;234(8):12809-20. doi:10.1002/jcp.27915.

33. Hu S, Zhang J, Guo G, Zhang L, Dai J, Gao Y. Comprehensive analysis of GSEC/miR-101-3p/SNX16/PAPOLG axis in hepatocellular carcinoma. PLoS One. 2022 Apr 28;17(4):e0267117. doi:10.1371/journal.pone.0267117.

34. Liu R, Ju C, Zhang F, Tang X, Yan J, Sun J, et al. LncRNA GSEC promotes the proliferation, migration and invasion by sponging miR-588/EIF5A2 axis in osteosarcoma. Biochem Biophys Res Commun. 2020 Nov 5;532(2):300-7. doi:10.1016/j.bbrc.2020.08.056.

35. Zhang J, Du C, Zhang L, Wang Y, Zhang Y, Li J. lncRNA GSEC Promotes the Progression of Triple Negative Breast Cancer (TNBC) by Targeting the miR-202-5p/AXL Axis. Onco Targets Ther. 2021 Apr 20;14:2747-59. doi:10.2147/OTT.S293832.

36. Liu P, Zhou L, Chen H, He Y, Li G, Hu K. Identification of a novel intermittent hypoxia-related prognostic lncRNA signature and the ceRNA of lncRNA GSEC/miR-873-3p/EGLN3 regulatory axis in lung adenocarcinoma. PeerJ. 2023 Oct 10;11:e16242. doi:10.7717/peerj.16242.

37. Yang K, Liu H, Li JH. A methylation-related lncRNA-based prediction model in lung adenocarcinomas. Clin Respir J. 2024 Aug;18(8):e13753. doi:10.1111/crj.13753.

38. Hu J, Tian S, Liu Q, Hou J, Wu J, Wang X, et al. A prognostic signature of Glutathione metabolism-

associated long non-coding RNAs for lung adenocarcinoma with immune microenvironment insights. Front Immunol. 2025 Feb 10;16:1477437. doi:10.3389/fimmu.2025.1477437.

39. Li Y, Li X, Yu Z. Novel methylation-related long non-coding RNA clinical outcome prediction method: the clinical phenotype and immune infiltration research in low-grade gliomas. Front Oncol. 2023 May 9;13:1177120. doi:10.3389/fonc.2023.1177120.

40. Hu J, Tian S, Liu Q, Hou J, Wu J, Wang X, et al. A prognostic signature of Glutathione metabolism-associated long non-coding RNAs for lung adenocarcinoma with immune microenvironment insights. Front Immunol. 2025 Feb 10;16:1477437. doi:10.3389/fimmu.2025.1477437.

41. Miló Valdés CA, Pérez Acevedo LC, Vitón Castillo AA. Utility of immunoinformatics in epitope mapping for vaccine and therapeutic design. eVitroKhem. 2025;4:152. https://doi.org/10.56294/evk2025152

42. Song J, Sun Y, Cao H, Liu Z, Xi L, Dong C, et al. A novel pyroptosis-related lncRNA signature for prognostic prediction in patients with lung adenocarcinoma. Bioengineered. 2021 Dec;12(1):5932-49. doi:10.1080/21655979.2021.1972078.

43. Liu A, Wang X, Hu L, Yan D, Yin Y, Zheng H, et al. A predictive molecular signature consisting of lncRNAs associated with cellular senescence for the prognosis of lung adenocarcinoma. PLoS One. 2023 Jun 23;18(6):e0287132. doi:10.1371/journal.pone.0287132.

44. Vitón Castillo AA, Miló Valdés CA, Pérez Acevedo LC. Biological databases useful for epitope mapping and immune response simulation. eVitroKhem. 2025;4:300. https://doi.org/10.56294/evk2025300

45. Pires A, Burnell S, Gallimore A. Exploiting ECM remodelling to promote immune-mediated tumour destruction. Curr Opin Immunol. 2022 Feb;74:32-8. doi:10.1016/j.coi.2021.09.006.

46. Huang D, Chen J, Yang L, Ouyang Q, Li J, Lao L, et al. NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. Nat Immunol. 2018 Oct;19(10):1112-25. doi:10.1038/s41590-018-0207-y.

47. Liu C, Shen A, Song J, Cheng L, Zhang M, Wang Y, et al. LncRNA-CCAT5-mediated crosstalk between Wnt/β-Catenin and STAT3 signaling suggests novel therapeutic approaches for metastatic gastric cancer with high Wnt activity. Cancer Commun (Lond). 2024 Jan;44(1):76-100. doi:10.1002/cac2.12507.

48. Xu Z, Wang Q, Zhang Y, Li X, Wang M, Zhang Y, et al. Exploiting tertiary lymphoid structures gene signature to evaluate tumor microenvironment infiltration and immunotherapy response in colorectal cancer. Front Oncol. 2024 May 23;14:1383096. doi:10.3389/fonc.2024.1383096.

49. Sun M, Geng D, Li S, Chen Z, Zhao W. LncRNA PART1 modulates toll-like receptor pathways to influence cell proliferation and apoptosis in prostate cancer cells. Biol Chem. 2018 Mar 28;399(4):387-95. doi:10.1515/hsz-2017-0255.

50. Chen Z, Qiao S, Yang L, Sun M, Li B, Lu A, et al. Mechanistic Insights into the Roles of the IL-17/IL-17R Families in Pancreatic Cancer. Int J Mol Sci. 2023 Aug 31;24(17):13539. doi:10.3390/ijms241713539.

51. Razi S, Baradaran Noveiry B, Keshavarz-Fathi M, Rezaei N. IL-17 and colorectal cancer: From carcinogenesis to treatment. Cytokine. 2019 Apr;116:7-12. doi: 10.1016/j.cyto.2018.12.021.

52. Festekdjian T, Bonavida B. Targeting the Depletion of M2 Macrophages: Implication in Cancer Immunotherapy. Crit Rev Oncog. 2024;29(4):55-73. doi: 10.1615/CritRevOncog.2024053580.

53. Zhou W, Feng Y, Lin C, Chao CK, He Z, Zhao S, et al. Yin Yang 1-Induced Long Noncoding RNA DUXAP9 Drives the Progression of Oral Squamous Cell Carcinoma by Blocking CDK1-Mediated EZH2 Degradation. Adv Sci (Weinh). 2023 Sep;10(25):e2207549. doi: 10.1002/advs.202207549.

54. Shi L, Yang Y, Li M, Li C, Zhou Z, Tang G, et al. LncRNA IFITM4P promotes immune escape by up-regulating PD-L1 via dual mechanism in oral carcinogenesis. Mol Ther. 2022 Apr 6;30(4):1564-1577. doi: 10.1016/j.

ymthe.2022.01.003.

FINANCING

This study was supported by Natural Science Foundation of Inner Mongolia Autonomous Region of china (Grant number 2024QN08053).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Data curation: Od Bayarsaikhan, Ganbayar Batmunkh.
Formal analysis: Xu Wu.
Research: Deleheibateer.
Methodology: Deleheibateer, Od Bayarsaikhan.
Project management: Shiirevnyamba Avirmed.
Software: Ganbayar Batmunkh, Xu Wu.
Validation: Xingan Zhou.
Display: Xingan Zhou.
Drafting - original draft: Deleheibateer.
Writing - proofreading and editing: Shiirevnyamba Avirmed.