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The High Expression of *EXOSC3* in OSCC is Associated with Poor Prognosis and Immune Infiltration

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Abstract: Oral squamous cell carcinoma (OSCC) is the most common malignant tumor in the oral and maxillofacial region, primarily affecting the tongue, gingiva, oral cavity, buccal mucosa, and floor of the mouth. It exhibits high rates of recurrence and metastasis, contributing to a poor prognosis for patients. Identifying molecular markers associated with OSCC holds significant value for advancing its diagnosis, treatment, and prognosis. *Exosome Component 3* (*EXOSC3*) is a protein-coding gene involved in the auto-degradation of E3 ubiquitin ligase COP 1 and rRNA processing in the nucleus and cytoplasmic sol. This gene plays a crucial role in diseases such as colon cancer and non-small cell lung cancer. Bioinformatics analysis revealed that *EXOSC3* expression is significantly elevated in OSCC and is associated with poor patient prognosis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses indicate that *EXOSC3* is strongly linked to the cytokine-cytokine receptor interaction, Toll-like receptor signaling pathway, and JAK-STAT signaling pathway. Moreover, immune infiltration analysis demonstrated a significant association between *EXOSC3* expression and immune cell subset infiltration, as well as immune checkpoint expression, underscoring its importance in OSCC. However, further research is required to elucidate the specific role of *EXOSC3* in OSCC diagnosis and treatment. A comprehensive investigation into the mechanisms of *EXOSC3* in OSCC may reveal new potential targets for improving the diagnosis and treatment of this malignancy.

Keywords: *EXOSC3*; Oral squamous cell carcinoma; Immune microenvironment; Immune checkpoint

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1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignant tumor originating from the epithelium of the oral mucosa, accounting for over 90% of all oral cancers [1]. Various factors, including smoking, alcohol consumption, viral infections, environmental influences, and genetic predispositions, are associated with OSCC development [2]. The unique anatomical characteristics of the oral and maxillofacial region, characterized by abundant blood supply and lymphatic networks, render it susceptible to lymph node metastasis, a key factor influencing prognosis. Additionally, the complex structural nature of the maxillofacial region causes significant damage to aesthetics and

functional abilities, such as speech, thereby severely impacting the quality of life of affected individuals [3]. Despite advancements in treatment modalities, including radiotherapy, chemotherapy, surgery, and immunotherapy, the prognosis for patients in advanced stages remains suboptimal [4]. Thus, exploring novel diagnostic and therapeutic targets is essential for addressing the underlying mechanisms of OSCC development.

Exosome Component 3 (*EXOSC3*) is a protein-coding gene implicated in the auto-degradation of E3 ubiquitin ligase COP 1 and rRNA processing within the nucleus and cytoplasmic sol. Clinically, *EXOSC3* is associated with diseases such as cerebellar ataxia type 1B and non-syndromic cerebellar ataxia, as well as the development of various tumors. For instance, MYD88 regulates *EXOSC3* to influence colon cancer progression [5]. In non-small cell lung cancer, functional variants of *EXOSC3* are associated with patient prognosis and survival [6]. However, studies investigating the role of *EXOSC3* in OSCC remain limited. Therefore, a detailed exploration of its function in OSCC may provide new insights into potential therapeutic targets.

This study utilizes bioinformatics analysis of transcriptome data from The Cancer Genome Atlas (TCGA) database to examine differences in *EXOSC3* expression between OSCC and adjacent tissues. The impact of these expression differences on OSCC patient prognosis is assessed through survival curve analysis. Co-expression analyses within the TCGA-OSCC cohort are conducted to identify potential functional networks involving *EXOSC3*. Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses are employed to explore the pathways through which *EXOSC3* may influence OSCC progression. Immune infiltration and drug sensitivity analyses further evaluate the potential impact of *EXOSC3* on immunotherapy and chemotherapy responses.

2. Materials and methods

2.1. Sample data and clinical information download

Transcriptome data and clinical information for OSCC patients were downloaded from TCGA, comprising data from 346 tumor tissues and 32 normal tissues [7].

2.2. ROC analysis

To evaluate the diagnostic performance of *EXOSC3* in the TCGA-OSCC cohort, the “pROC” R package was used to analyze the expression levels and clinical information of OSCC cases. The sensitivity of EXOSC3 in OSCC was assessed, and the area under the curve (AUC) was calculated.

2.3. Survival analysis

The impact of *EXOSC3* expression levels on OSCC patient prognosis was investigated by excluding cases with missing clinical information. Patients were categorized into high- and low-expression groups based on *EXOSC3* expression levels. Survival analysis and visualization were performed using the “survival” R package.

2.4. Co-expression analysis

To identify co-expressed genes associated with *EXOSC3* in the TCGA-OSCC cohort, correlation analysis was conducted using the “limma” R package. Pearson’s correlation test was employed to calculate correlation coefficients, with a significance threshold of $P < 0.001$. The results were visualized using scatter plots.

2.5. Differential expression analysis

To identify differentially expressed genes (DEGs) associated with *EXOSC3*, OSCC patients were divided into

high- and low-expression groups based on the median expression level of EXOSC3. Differential analysis was performed using the "limma" R package, with selection criteria of |logFC| > 1 and $P < 0.05$. The top 50 DEGs were visualized using a heatmap [8].

2.6. Functional enrichment analysis

The potential roles of *EXOSC3* in OSCC were explored through GO and KEGG enrichment analyses of DEGs associated with *EXOSC3*. The analyses were conducted using the "clusterProfiler" R package, with a significance threshold of $P < 0.05$. The results were visualized using the "ggplot2" R package [9].

2.7. Immune infiltration analysis

The impact of *EXOSC3* on immune cell subsets in OSCC was assessed using the CIBERSORT algorithm to calculate immune cell scores and evaluate immune infiltration. Spearman correlation analysis was employed, with a significance threshold of $P < 0.05$, to determine the relationship between *EXOSC3* expression and immune cell subsets [10].

2.8. Immune checkpoint analysis

To investigate the role of *EXOSC3* in immunotherapy, Pearson correlation analysis was conducted on 47 immune checkpoint genes, with a significance threshold of $P < 0.001$.

2.9. Drug sensitivity analysis

The effect of *EXOSC3* on chemotherapy drug sensitivity in the TCGA-OSCC cohort was evaluated using the "pRRophetic" R package to analyze the IC_{50} values of chemotherapy drugs for each sample. Patients were divided into high- and low-expression groups based on the median *EXOSC3* expression level, and differences in IC_{50} values were analyzed using the Wilcoxon test. The results were visualized using the "limma" R package.

2.10. Statistical analysis

All statistical analyses were conducted using R (v4.3.2, R Foundation for Statistical Computing). A *P*-value of < 0.05 was considered statistically significant.

3. Results

3.1. Abnormal expression of EXOSC3 in OSCC and its association with poor prognosis

Transcriptome data and relevant clinical information from the TCGA-OSCC cohort were analyzed. Using the "limma" R package, it was found that *EXOSC3* expression was significantly elevated in OSCC tissues compared to normal tissues (**Figure 1A**). To confirm this finding, only cases with paired data were analyzed, revealing consistent results; *EXOSC3* expression was significantly higher in paired OSCC tissues compared to paired normal tissues (**Figure 1B**).

To further explore the role of *EXOSC3* in OSCC, an ROC curve was plotted for the TCGA-OSCC cohort. The area under the curve (AUC) was 0.870, with a 95% confidence interval of 0.816–0.922, indicating that *EXOSC3* exhibits good diagnostic efficacy for OSCC (**Figure 1C**). Kaplan-Meier survival analysis revealed that patients with high *EXOSC3* expression had significantly poorer overall survival (**Figure 1D**). Additionally, higher *EXOSC3* expression levels were positively associated with more advanced tumor stages, including the T stage.

3.2. Gene co-expression analysis of EXOSC3 in OSCC

Given the observed association between elevated EXOSC3 expression and poor prognosis in OSCC, gene co-expression analysis was performed using the "limma" R package. Six genes were identified as strongly correlated with *EXOSC3*: *APTX*, *CLTA*, *RPS6*, *MELK*, *DNAJA1*, and *STOML2* (**Figures 2A–F**).

3.3. Functional analysis of EXOSC3 in OSCC

To investigate the functional roles of *EXOSC3* in OSCC, samples were categorized into high and low expression groups based on the median *EXOSC3* expression level. Differential expression analysis using the "limma" R package identified DEGs associated with *EXOSC3*. The top 50 DEGs were visualized using a heatmap (**Figure 3A**).

GO enrichment analysis revealed that *EXOSC3* was involved in various cellular biological processes, including the humoral immune response, activation of natural killer cells in immune responses, negative regulation of activated T cell proliferation, and natural killer cell activation (**Figures 3B** and **C**). KEGG enrichment analysis identified its association with key pathways such as cytokine-cytokine receptor interaction, natural killer cell-mediated cytotoxicity, the Toll-like receptor signaling pathway, and the JAK-STAT signaling pathway. These pathways are implicated in tumorigenesis and progression (**Figures 3D** and **E**). These findings suggest that *EXOSC3* may play a pivotal role in OSCC.

3.4. Association of EXOSC3 with the immune microenvironment in OSCC

Enrichment analysis indicated that *EXOSC3* is closely linked to immune cell activity, particularly involving natural killer cells and T cells. To further explore this relationship, the association between *EXOSC3* and the immune microenvironment in OSCC was assessed. Significant differences in stromal scores were observed between high and low *EXOSC3* expression groups, suggesting that *EXOSC3* expression levels may influence stromal cell content in the tumor microenvironment (**Figure 4A**).

Immune cell infiltration was analyzed using the CIBERSORT algorithm. Significant differences were observed in immune cell subsets, including T cells CD8, T cells CD4 memory activated, T cells follicular helper, macrophages M0, and macrophages M1, between high and low *EXOSC3* expression groups (**Figure 4B**). Spearman correlation analysis further revealed significant correlations of *EXOSC3* with macrophages M1, T cells CD8, T cells CD4 memory activated, T cells follicular helper, monocytes, and macrophages M0 (**Figures 4C–F**).

3.5. Impact of EXOSC3 expression on tumor-related treatments

The role of *EXOSC3* in immunotherapy was evaluated by examining its correlation with 47 immune checkpoint genes. Positive correlations were identified with *CD40*, *TNFRSF25*, *CD70*, *LAG3*, *PDCD1*, *IDO1*, *HAVCR2*, *CD274*, *PDCD1LG2*, and *CTLA4*, highlighting the potential role of *EXOSC3* in immune regulation and immunotherapy (**Figures 5A** and **B**).

To assess its impact on chemotherapy sensitivity, data from the Cancer Genome Project (CGP) database were analyzed. A significant correlation was found between *EXOSC3* expression levels and sensitivity to various chemotherapy drugs, including 5-Fluorouracil, AKT inhibitor VIII, Bexarotene, and Bleomycin (**Figures 5C–F**).

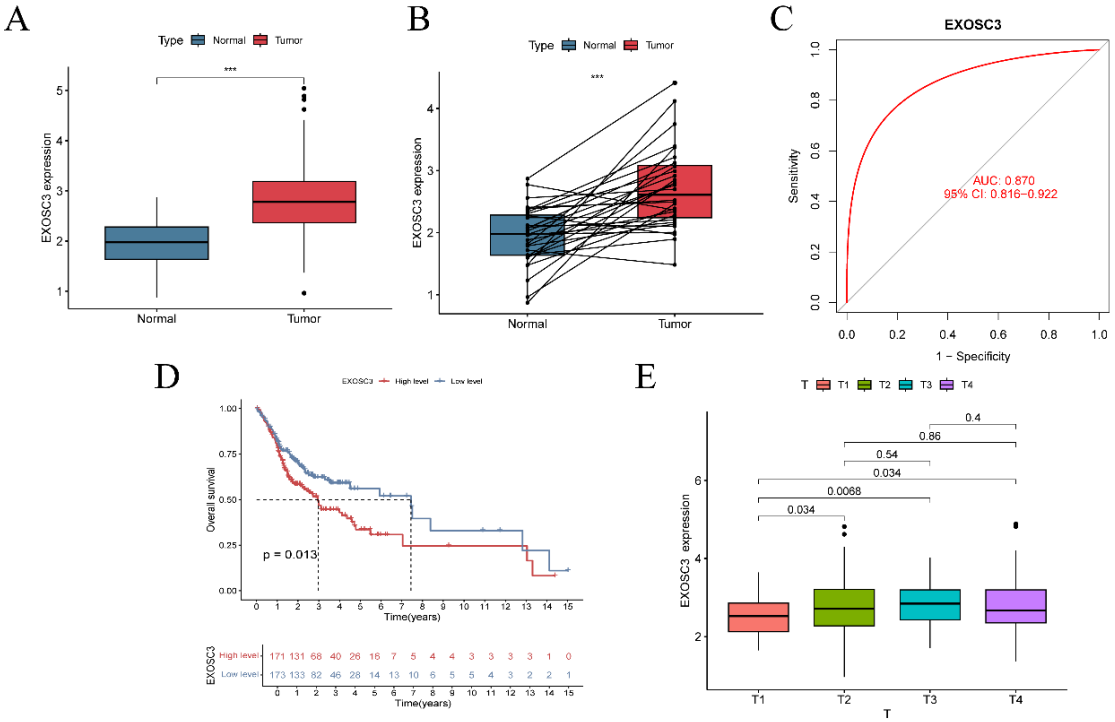

Figure 1. High expression of *EXOSC3* in OSCC is associated with poor prognosis. **(A)** In the TCGA-OSCC cohort, *EXOSC3* expression was significantly higher in OSCC tissues compared to adjacent normal tissues (***$P < 0.001$). **(B)** Paired analysis of adjacent normal tissues and OSCC tissues also demonstrated significantly increased *EXOSC3* expression in OSCC (***$P <$ 0.001). **(C)** Receiver operating characteristic curve for *EXOSC3* in the TCGA-OSCC cohort, indicating its diagnostic efficacy. **(D)** Kaplan-Meier survival curve illustrating overall survival differences between high-expression and low-expression groups of *EXOSC3*. **(E)** Correlation between T stage and *EXOSC3* expression in patients from the TCGA-OSCC cohort.

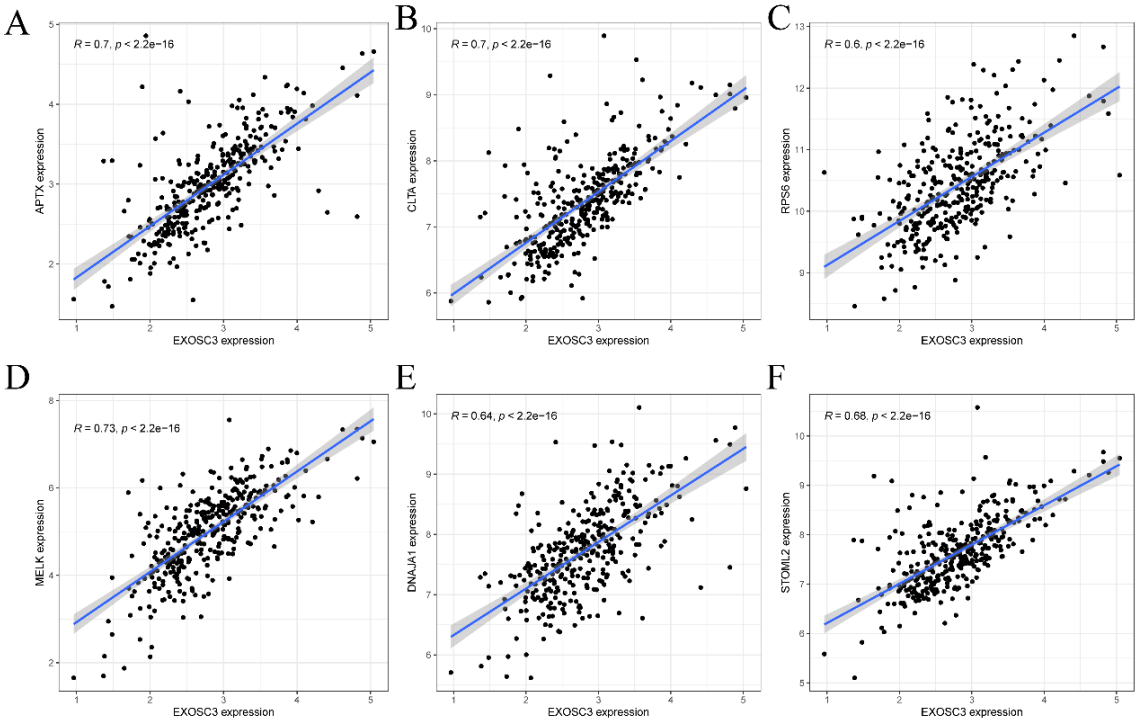

Figure 2. Gene co-expression of *EXOSC3* in OSCC. **(A–F)** Identification of six genes co-expressed with *EXOSC3* in the TCGA-OSCC cohort.

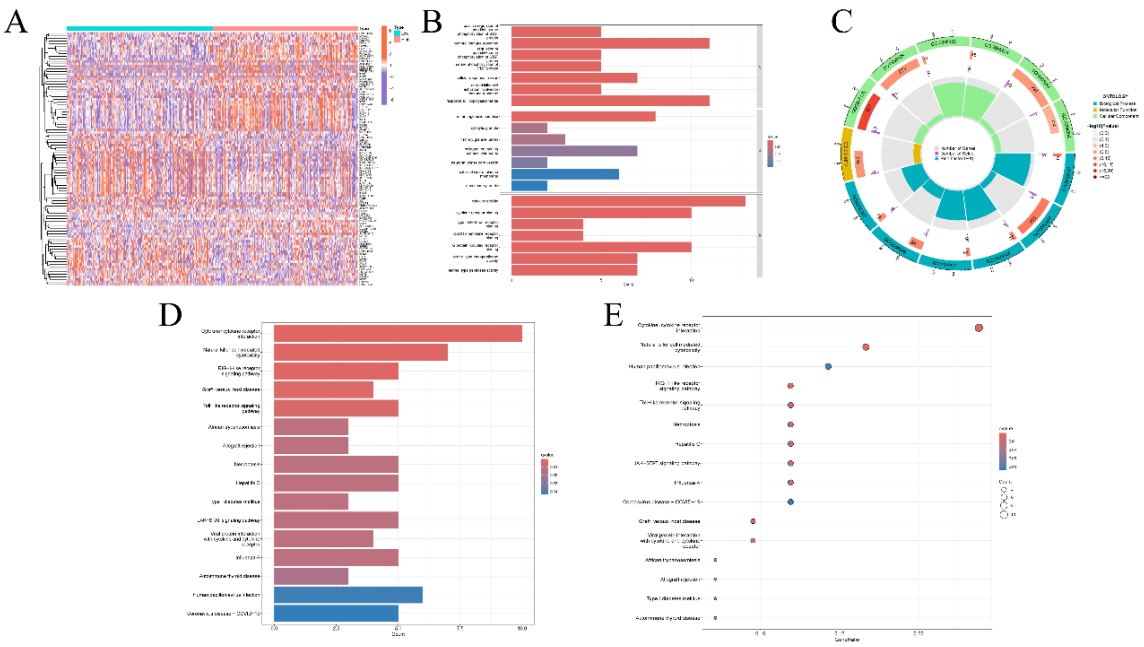

Figure 3. Functional role of *EXOSC3* in OSCC. **(A)** Heatmap of differentially expressed genes associated with *EXOSC3* in the TCGA-OSCC cohort. **(B–C)** Results of Gene Ontology enrichment analysis. **(D–E)** Results of Kyoto Encyclopedia of Genes and Genomes enrichment analysis.

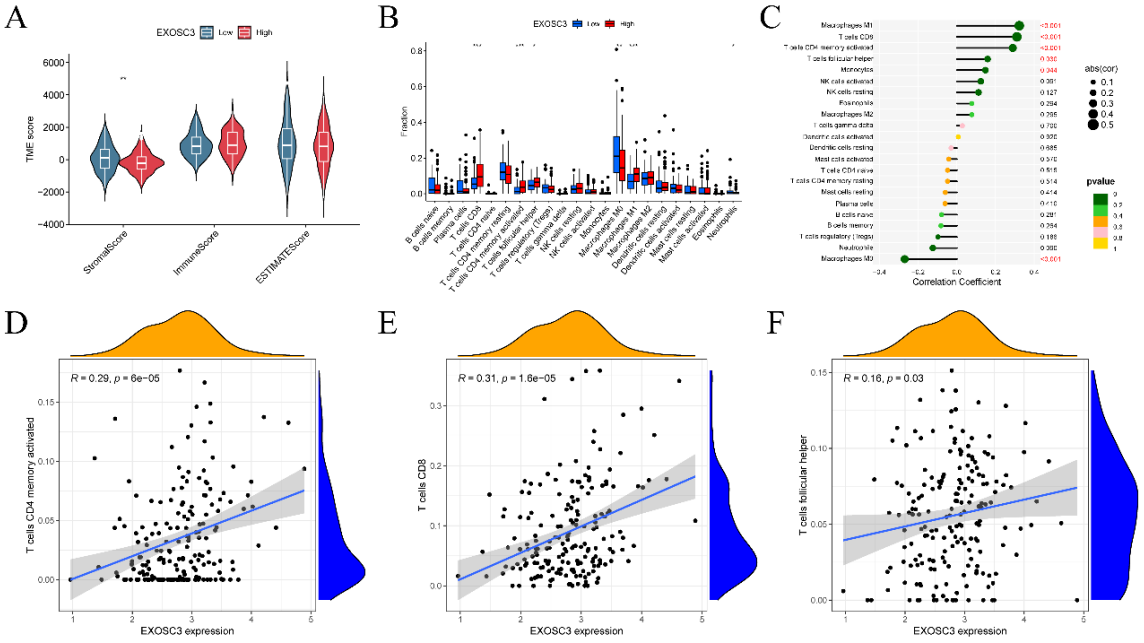

Figure 4. The role of *EXOSC3* in the immune microenvironment. **(A)** Assessment of *EXOSC3* in the immune microenvironment of OSCC. **(B)** Differences in various immune cell populations between high and low *EXOSC3* expression groups in OSCC. **(C–F)** Correlations between *EXOSC3* expression and specific immune cell populations.

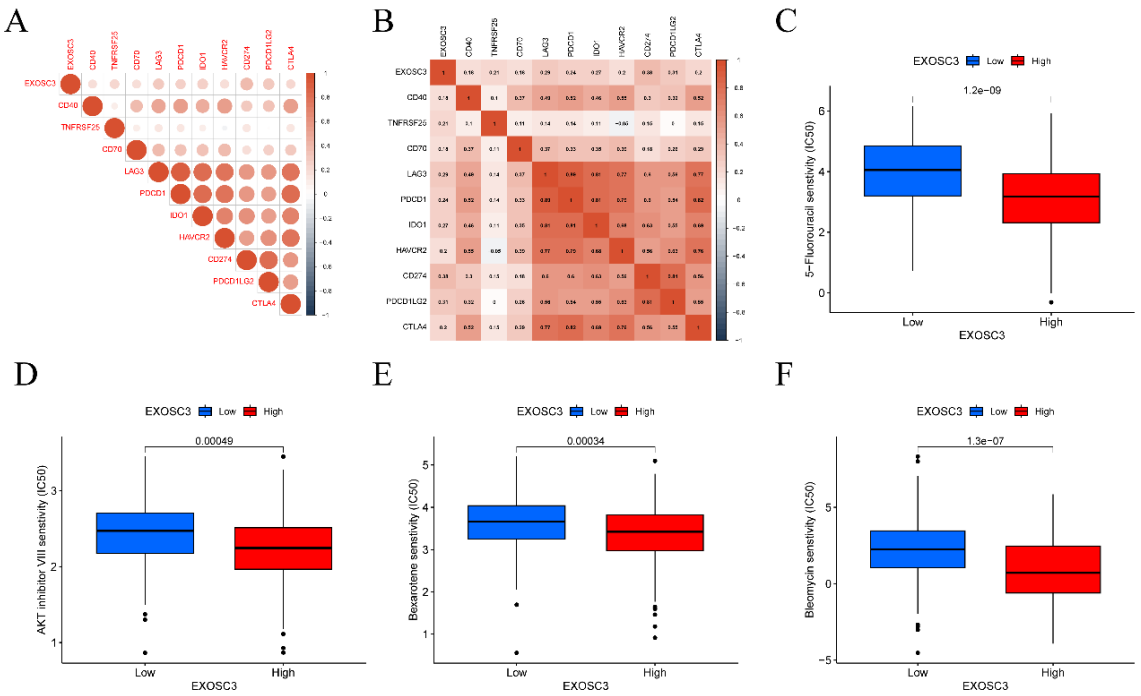

Figure 5. Correlation of *EXOSC3* expression levels with immune checkpoints and chemotherapy drugs in OSCC. **(A–B)** Analysis of correlations between *EXOSC3* expression and immune checkpoint genes. **(C)** Association between *EXOSC3* expression and sensitivity to 5-Fluorouracil. **(D)** Association between *EXOSC3* expression and sensitivity to AKT inhibitor VIII. **(E)** Association between *EXOSC3* expression and sensitivity to Bexarotene. **(F)** Association between *EXOSC3* expression and sensitivity to Bleomycin.

4. Discussion

OSCC is a prevalent type of squamous cell carcinoma in the head and neck region, predominantly originating from the stratified squamous epithelium of the oral mucosa and accounting for up to 90% of oral cancers [11]. Commonly affected areas include the tongue, buccal mucosa, gingiva, and floor of the mouth. Due to the unique anatomical characteristics of the oral and maxillofacial region, including a rich blood supply and lymphatic drainage, OSCC often presents with a poor prognosis [12]. Despite advances in radiotherapy, chemotherapy, surgery, immunotherapy, and combination therapies, the 5-year survival rate for OSCC under conventional treatment models remains suboptimal due to high recurrence and metastasis rates [13]. Consequently, there is an urgent need to identify novel diagnostic and therapeutic targets to improve early detection and treatment outcomes.

EXOSC3 is a protein-coding gene encoding a non-catalytic component of human exosomes. This complex exhibits 3'-5' exoribonuclease activity, playing a crucial role in RNA processing and degradation [14]. Its primary physiological functions include RNA binding and exoribonuclease activity. *EXOSC3* is also implicated in diseases such as spinocerebellar ataxia type 1B and non-syndromic spinocerebellar ataxia. In cancer development, *EXOSC3* has been shown to play a significant role. Protein sequencing studies have linked *EXOSC3* to pancreatic cancer, and in gastric cancer, *EXOSC3* significantly influences treatment outcomes based on risk scores [15]. Furthermore, *EXOSC3* is considered a potential molecular biomarker for lung cancer in Chinese populations [16]. However, limited research exists on the role of *EXOSC3* in OSCC, necessitating further investigation into its potential functions.

Bioinformatics analysis of TCGA-OSCC cohort data revealed that *EXOSC3* is significantly overexpressed in OSCC tissues, a finding corroborated in paired OSCC samples. To determine whether this overexpression influences diagnostic and prognostic outcomes, ROC analysis and Kaplan-Meier survival curve analysis were conducted. The ROC curve demonstrated an AUC of 0.870, indicating high diagnostic efficacy in the TCGA-OSCC cohort. Similarly, Kaplan-Meier survival analysis showed that patients with high *EXOSC3* expression exhibited poorer prognosis compared to those with low expression. Clinical data analysis further revealed that increased *EXOSC3* expression correlated with advanced T stage. These findings suggest that *EXOSC3* overexpression is associated with poor prognosis and higher clinical stages in OSCC.

To explore the functional implications of *EXOSC3*, gene co-expression analysis was conducted using TCGA-OSCC cohort data. Six genes—*APTX*, *CLTA*, *RPS6*, *MELK*, *DNAJA1*, and *STOML2*—were identified as positively correlated with *EXOSC3*. These genes have established roles in tumor biology: *APTX* serves as a prognostic marker for cancer post-kidney transplantation [17], *CLTA* promotes hepatocellular carcinoma progression via small extracellular vesicles [18], and *RPS6* contributes to drug resistance in gastric cancer through *NRF2*. Additionally, *MELK* regulates *DLAT* in mitochondrial mediation of liver cancer, *DNAJA1* activates the mutant p53/NF-κB pathway to promote breast cancer proliferation and metastasis, and *STOML2* facilitates colorectal cancer progression via the MAPK signaling pathway and interaction with *PHB*. The co-expression of these tumor-associated genes with *EXOSC3* suggests that *EXOSC3* may exert its oncogenic effects through these pathways.

To further elucidate the potential pathways involved, GO and KEGG enrichment analyses were performed. GO enrichment analysis identified cellular immune activities associated with *EXOSC3*, including the humoral immune response, natural killer cell activation in immune response, negative regulation of activated T cell proliferation, and natural killer cell activation. KEGG enrichment analysis highlighted several key pathways, such as cytokine-cytokine receptor interaction, natural killer cell-mediated cytotoxicity, Toll-like receptor signaling, and JAK-STAT signaling. The Toll-like receptor signaling pathway has been implicated in OSCC pathogenesis [19], while the JAK-STAT pathway has been shown to promote OSCC progression and invasion [20].

The relationship between *EXOSC3* and immune infiltration in OSCC was analyzed to verify its role in the tumor immune microenvironment. Significant differences in stromal scores were observed between high and low *EXOSC3* expression groups, suggesting a potential impact of *EXOSC3* on stromal cell content in the tumor microenvironment. Immune cell infiltration analysis revealed associations between *EXOSC3* and specific immune cells, particularly T cells CD8 and T cells CD4 memory activated, which are known to influence tumorigenesis and progression.

In terms of therapeutic implications, several immune checkpoint genes, including *CD40*, *TNFRSF25*, *CD70*, *LAG3*, *PDCD1*, *IDO1*, *HAVCR2*, *CD274*, *PDCD1LG2*, and *CTLA4*, were positively correlated with *EXOSC3* expression. This suggests a potential role for *EXOSC3* in immunotherapy efficacy for OSCC. However, further experimental validation is necessary to determine whether *EXOSC3* can serve as a biomarker for immunotherapy. While surgery remains the primary treatment modality for OSCC, chemotherapy is an essential adjunct. In this study, lower *EXOSC3* expression levels were associated with higher sensitivity to chemotherapy agents such as 5-Fluorouracil, AKT inhibitor VIII, Bexarotene, and Bleomycin. These findings may expand the range of therapeutic options and guide the development of new treatment strategies.

5. Conclusion

In summary, *EXOSC3* is significantly overexpressed in OSCC tissues, and its elevated expression is closely associated with poor patient prognosis and the advancement of clinical stages. *EXOSC3* may exert its effects through interactions with multiple co-expressed genes and critical biological pathways. Furthermore, its high expression is linked to alterations in the tumor immune microenvironment and immune cell infiltration. These findings highlight the potential of *EXOSC3* as a promising target for novel therapeutic approaches, including immune checkpoint therapy and chemotherapy.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Bugshan A, Farooq I, 2020, Oral Squamous Cell Carcinoma: Metastasis, Potentially Associated Malignant Disorders, Etiology and Recent Advancements in Diagnosis. F1000Res, 9: 229. https://doi.org/10.12688/f1000research.22941.1

[2] Chai A, Lim KP, Cheong SC, 2020, Translational Genomics and Recent Advances in Oral Squamous Cell Carcinoma. Semin Cancer Biol, 61: 71–83. https://doi.org/10.1016/j.semcancer.2019.09.011

[3] Ma X, Yang R, Li H, et al., 2024, Role of Exosomes in the Communication and Treatment Between OSCC and Normal Cells. Heliyon, 10(7): e28148. https://doi.org/10.1016/j.heliyon.2024.e28148

[4] Ramqvist T, Dalianis T, 2011, An Epidemic of Oropharyngeal Squamous Cell Carcinoma (OSCC) Due to Human Papillomavirus (HPV) Infection and Aspects of Treatment and Prevention. Anticancer Res, 31(5): 1515–1519.

[5] Eggens VR, Barth PG, Niermeijer JM, et al., 2014, EXOSC3 Mutations in Pontocerebellar Hypoplasia Type 1: Novel Mutations and Genotype-Phenotype Correlations. Orphanet J Rare Dis, 9: 23. https://doi.org/10.1186/1750-1172-9-23

[6] Lu G, Liu H, Wang H, et al., 2024, Potentially Functional Variants of INPP5D and EXOSC3 in Immunity B Cell-Related Genes are Associated with Non-Small Cell Lung Cancer Survival. Front Immunol, 15: 1440454. https://doi.org/10.3389/fimmu.2024.1440454

[7] Tomczak K, Czerwinska P, Wiznerowicz M, 2015, The Cancer Genome Atlas (TCGA): An Immeasurable Source of Knowledge. Contemp Oncol (Pozn), 19(1A): A68–A77. https://doi.org/10.5114/wo.2014.47136

[8] Ritchie ME, Phipson B, Wu D, et al., 2015, Limma Powers Differential Expression Analyses for RNA-Sequencing and Microarray Studies. Nucleic Acids Res, 43(7): e47. https://doi.org/10.1093/nar/gkv007

[9] Xu S, Hu E, Cai Y, et al., 2024, Using clusterProfiler to Characterize Multiomics Data. Nat Protoc, 19(11): 3292–3320. https://doi.org/10.1038/s41596-024-01020-z

[10] Chen B, Khodadoust MS, Liu CL, et al., 2018, Profiling Tumor Infiltrating Immune Cells with CIBERSORT. Methods Mol Biol, 1711: 243–259. https://doi.org/10.1007/978-1-4939-7493-1_12

[11] Oyeyemi BF, Kaur US, Paramraj A, et al., 2023, Microbiome Analysis of Saliva from Oral Squamous Cell Carcinoma (OSCC) Patients and Tobacco Abusers with Potential Biomarkers for Oral Cancer Screening. Heliyon, 9(11): e21773. https://doi.org/10.1016/j.heliyon.2023.e21773

[12] Liu B, Si W, Wei B, et al., 2023, PTP4A1 Promotes Oral Squamous Cell Carcinoma (OSCC) Metastasis Through Altered Mitochondrial Metabolic Reprogramming. Cell Death Discov, 9(1): 360. https://doi.org/10.1038/s41420-023-01657-x

[13] Mumtaz M, Bijnsdorp IV, Bottger F, et al., 2022, Secreted Protein Markers in Oral Squamous Cell Carcinoma (OSCC).

Clin Proteomics, 19(1): 4. https://doi.org/10.1186/s12014-022-09341-5

[14] Szeto CH, Rubin S, Sidlow R, 2023, Homozygous EXOSC3 c.395A>C Variants in Pontocerebellar Hypoplasia Type 1B: A Sibling Pair with Childhood Lethal Presentation and Literature Review. Cureus, 15(5): e39226. https://doi.org/10.7759/cureus.39226

[15] Bauer L, Hapfelmeier A, Blank S, et al., 2018, A Novel Pretherapeutic Gene Expression-Based Risk Score for Treatment Guidance in Gastric Cancer. Ann Oncol, 29(1): 127–132. https://doi.org/10.1093/annonc/mdx685

[16] Xie Y, Wu H, Hu W, et al., 2022, Identification of Hub Genes of Lung Adenocarcinoma Based on Weighted Gene Co-Expression Network in Chinese Population. Pathol Oncol Res, 28: 1610455. https://doi.org/10.3389/pore.2022.1610455

[17] Fu Q, Yang F, Liao M, et al., 2019, Rap GTPase Interactor: A Potential Marker for Cancer Prognosis Following Kidney Transplantation. Front Oncol, 9: 737. https://doi.org/10.3389/fonc.2019.00737

[18] Xu Y, Yao Y, Yu L, et al., 2023, Clathrin Light Chain A Facilitates Small Extracellular Vesicle Uptake to Promote Hepatocellular Carcinoma Progression. Hepatol Int, 17(6): 1490–1499. https://doi.org/10.1007/s12072-023-10562-5

[19] Di Lorenzo A, Bolli E, Tarone L, et al., 2020, Toll-Like Receptor 2 at the Crossroad Between Cancer Cells, the Immune System, and the Microbiota. Int J Mol Sci, 21(24): 9418. https://doi.org/10.3390/ijms21249418

[20] Shao F, Pang X, Baeg GH, 2021, Targeting the JAK/STAT Signaling Pathway for Breast Cancer. Curr Med Chem, 28(25): 5137–5151. https://doi.org/10.2174/0929867328666201207202012