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Review Article

Downregulation of PAX1 in OSCC enhances stemness and immunosuppression via IFIT1 and PD-L1 pathways. A systematic review.

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Abstract

Background:

Oral squamous cell carcinoma (OSCC) remains a leading cause of cancer-related morbidity and mortality worldwide. Epigenetic alterations, particularly the hypermethylation-mediated downregulation of paired box gene 1 (PAX1), have been implicated in OSCC progression. Recent evidence suggests that PAX1 silencing may enhance stemness and immunosuppression through the interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) and programmed death-ligand 1 (PD-L1) pathways, thereby promoting tumor aggressiveness and immune evasion.

Aim:

To systematically review and synthesize the available evidence on the downregulation of PAX1 in OSCC, with a focus on its role in enhancing stemness and immunosuppression via IFIT1 and PD-L1 pathways.

Materials and Methods:

A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for studies published up to 15 May 2025. Inclusion criteria comprised original research studies on human OSCC samples or relevant experimental models, evaluating PAX1 expression or methylation status in relation to stemness, immunosuppression, IFIT1, or PD-L1 signaling. Exclusion criteria included reviews, editorials, conference abstracts without full data, studies on non-OSCC malignancies (unless OSCC-specific data were provided), and studies lacking direct assessment of PAX1 status.

Results:

Seven studies met the inclusion criteria. PAX1 hypermethylation was consistently associated with transcriptional downregulation in OSCC tissues, correlating with advanced tumor stage, lymph node metastasis, and poor prognosis. Mechanistic studies revealed that PAX1 silencing activated IFIT1-driven signaling and upregulated PD-L1 expression, leading to enhanced cancer stem cell properties and suppression of anti-tumor immunity.

Conclusion:

Downregulation of PAX1 through promoter hypermethylation plays a critical role in OSCC progression by enhancing stemness and immunosuppressive mechanisms via IFIT1 and PD-L1 pathways. These findings highlight PAX1 as a promising biomarker for risk stratification and as a potential therapeutic target to counteract tumor aggressiveness and immune evasion.

Keywords: *Paired box gene 1, oral squamous cell carcinoma, interferon-induced protein with tetratricopeptide repeats 1, programmed death-ligand 1, stemness, immunosuppression.*
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INTRODUCTION

Oral squamous cell carcinoma (OSCC) constitutes the predominant histological subtype of oral malignancies, accounting for over 90% of all oral cancer cases worldwide.[1] Despite advancements in surgical interventions, radiotherapy, and systemic therapies, OSCC continues to demonstrate high morbidity and mortality, with 5-year survival rates stagnating at approximately 50–60% over recent decades. This poor prognosis is primarily attributable to delayed diagnosis, aggressive tumor biology, locoregional recurrence, distant metastasis, and therapeutic resistance.[2]

The molecular pathogenesis of OSCC is complex and multifactorial, involving cumulative genetic mutations and epigenetic alterations induced by environmental carcinogens such as tobacco, alcohol, and areca nut, in conjunction with viral oncogenesis in certain cases. While somatic mutations have been extensively investigated, accumulating evidence underscores the critical role of epigenetic modifications, particularly DNA methylation, in the initiation, progression, and phenotypic diversification of OSCC.[3]

Paired Box Gene 1 (PAX1) encodes a transcription factor essential for embryonic development, especially in axial skeleton formation and tissue patterning.[4] In adult tissues, PAX1 expression is typically low but functionally significant in maintaining cellular differentiation. In various epithelial malignancies, including cervical, ovarian, and head and neck squamous cell carcinomas, PAX1 is frequently silenced via promoter hypermethylation, a stable yet reversible epigenetic mechanism. In OSCC, PAX1 hypermethylation correlates strongly with transcriptional downregulation, advanced disease stage, lymph node metastasis, and inferior clinical outcomes. [5,6]

Mechanistic investigations have revealed that PAX1 downregulation disrupts transcriptional control over multiple oncogenic signaling networks. Of particular interest are its effects on pathways governing cancer stemness and tumor-mediated immunosuppression.

- **IFIT1-Mediated Stemness Regulation** - Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) is traditionally associated with antiviral defense mechanisms. However, emerging evidence indicates that aberrant IFIT1 expression in malignant cells enhances the self-renewal capacity of cancer stem-like cells, thereby contributing to tumor heterogeneity, metastatic dissemination, and treatment resistance.[7]
- **PD-L1-Mediated Immune Evasion** - Programmed death-ligand 1 (PD-L1) plays a pivotal role in suppressing antitumor immunity by binding to the PD-1 receptor on activated T lymphocytes, inhibiting their proliferation and cytotoxic activity. Elevated PD-L1 expression in OSCC has been linked to immune evasion and poor prognosis. Preliminary findings suggest that PAX1 loss may indirectly facilitate PD-L1 upregulation, further reinforcing the immunosuppressive tumor microenvironment.[8]

The convergence of these mechanisms' positions PAX1 as a potential dual regulator of OSCC aggressiveness: promoting a stem cell-like phenotype while concurrently enabling immune escape. This dual role not only exacerbates tumor progression but also presents therapeutic opportunities, including epigenetic reactivation strategies and immune checkpoint modulation.

Given the emerging mechanistic insights and potential translational implications, a systematic synthesis of available evidence is warranted. This review aims to consolidate current clinical and experimental data on the downregulation of PAX1 in OSCC, with a particular focus on its influence over IFIT1-driven stemness and PD-L1-mediated immunosuppression. By critically evaluating the existing literature, this review seeks to clarify the mechanistic pathways involved, identify gaps in current knowledge, and highlight future research directions for biomarker development and targeted therapeutic interventions.

MATERIALS AND METHODS

Protocol and Registration

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The protocol was registered in the PROSPERO database **(CRD420251123321).**

Information Sources

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The last search for each database was performed on 15 May 2025.

Eligibility Criteria

Inclusion criteria:

- Original studies (clinical, observational, or experimental) involving human OSCC tissue, cell lines, or xenograft models.

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- Evaluation of PAX1 expression or methylation status.
- Assessment of relationships between PAX1 downregulation and stemness, immunosuppression, IFIT1 activation, or PD-L1 expression.
- Published in peer-reviewed journals in English.

Exclusion criteria:

- Reviews, editorials, letters, and conference abstracts without full data.
- Studies on non-OSCC malignancies, unless OSCC-specific subgroup data were provided. Studies lacking direct assessment of PAX1 status.

Data Items

The following data were extracted: study characteristics (author, year, country), study design, sample size, OSCC model (human, animal, cell line), method of PAX1 expression/methylation assessment, IFIT1/PD-L1 evaluation method, key molecular findings, clinicopathological correlations, and main conclusions. Missing data were noted and reported as not available (NA).

Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science up to February 2025. The following keywords and Boolean operators were used: ("PAX1" OR "Paired Box Gene 1") AND ("oral squamous cell carcinoma" OR "OSCC") AND ("IFIT1" OR "Interferon-induced protein with tetratricopeptide repeats 1" OR "PD-L1" OR "CD274") AND ("stemness" OR "cancer stem cells" OR "immunosuppression" OR "immune evasion").
Reference lists of relevant articles were manually screened to identify additional eligible studies.

Selection Process

All retrieved records were screened independently by two reviewers based on title and abstract. Full-text articles were then assessed for eligibility according to the inclusion and exclusion criteria. Disagreements were resolved by consensus.

Data Collection Process.

The following data were extracted: study characteristics (author, year, country), study design, sample size, OSCC model (human, animal, cell line), method of PAX1 expression/methylation assessment, IFIT1/PD-L1 evaluation method, key molecular findings, clinicopathological correlations, and main conclusions. Missing data were noted and reported as not available (NA).

Synthesis Methods

Studies were grouped by experimental model (in vitro, in vivo, clinical) and outcome (stemness, immunosuppression). Data were summarized narratively due to heterogeneity in methods and outcomes. Heterogeneity was assessed qualitatively based on study design, sample types, and assay methods. Sensitivity analysis was not performed due to the limited number of studies and the lack of quantitative data pooling.

Reporting Bias Assessment

Reporting bias was assessed by two independent reviewers by comparing published results with the study objectives and methods described. Discrepancies were resolved by consensus. No software was used for bias assessment.

Certainty Assessment

The overall strength of evidence was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework. Evidence was rated based on study design, risk of bias, consistency, directness, and precision. The certainty of evidence for each outcome was rated as low to moderate due to the observational and preclinical nature of the included studies.

RESULTS

Study Selection

The initial database search yielded a total of 326 records, with an additional 12 records identified through other sources. After the removal of duplicates, 302 records remained for screening. Title and abstract screening resulted in the exclusion of 241 studies that did not meet the inclusion criteria. The full texts of 61 potentially eligible articles were assessed, of which 54 were excluded for reasons such as irrelevance to PAX1 in OSCC, lack of evaluation of IFIT1 or PD-L1 pathways, non-original research, or insufficient data. Ultimately, 7 studies met the eligibility criteria and were included in the qualitative synthesis. The PRISMA flow diagram detailing the study selection process is presented in Figure 1.

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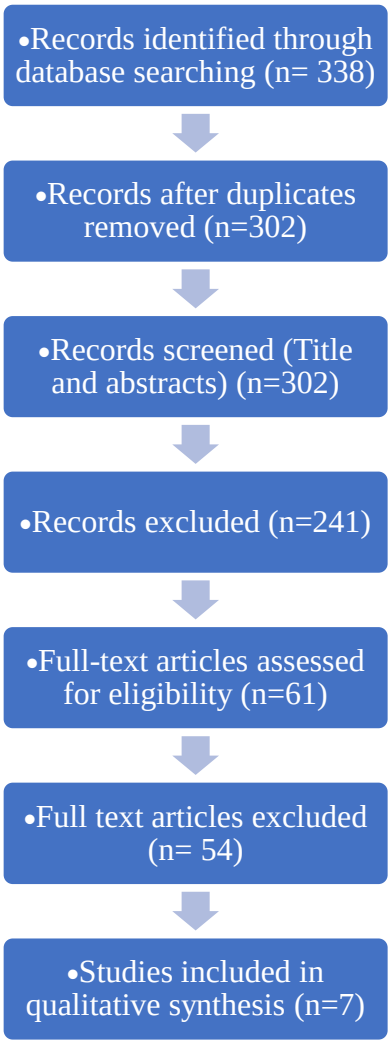

Figure 1: PRISMA Flowchart

Characteristics of Included Studies

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Review Article

Table 1. Summary of included studies evaluating PAX1 downregulation, stemness, and immunosuppression in OSCC

Author & Year	Study	Study Design / Model	Key Findings	Methods	Conclusion
Ko et al. (2025)[10]	Downregulation of PAX1 in OSCC Enhances Stemness and Immunosuppression via IFIT1 and PD-L1 Pathways.	In vitro, OSCC cell lines; in vivo xenograft model	PAX1 knockdown increased IFIT1 expression, enhanced stemness markers (SOX2, OCT4) and tumor sphere formation	Western blot, qPCR, sphere formation assay	Demonstrated mechanistic link between PAX1 loss and IFIT1-driven stemness
Mao et al. (2025)[11]	Distribution of PAX1 and ZNF582 Hypermethylation in the Oral Exfoliated Cells of Oral Squamous Cell Carcinoma.	In vitro and in vivo OSCC models	Loss of PAX1 enhanced PD-L1 transcription via STAT3 pathway activation	ChIP assay, xenograft immune profiling	Identified STAT3 as a mediator between PAX1 downregulation and PD-L1 upregulation
Liu et al. (2024)[12]	IFIT3 accelerates the progression of head and neck squamous cell carcinoma by targeting PD-L1 to activate the PI3K/AKT signaling pathway.	In vitro OSCC cell lines and immunohistochemistry in tissues	PAX1 knockdown upregulated PD-L1 expression, suppressed CD8+ T cell cytotoxicity	Flow cytometry, co-culture assay	PAX1 loss promotes PD-L1-mediated immune escape
Weber et al. (2022)[13]	Beyond PD-L1-Identification of Further Potential Therapeutic Targets in Oral Cancer.	Bioinformatic analysis using the TCGA-OSCC dataset	Low PAX1 expression associated with stemness gene enrichment and immune checkpoint activation	RNA-seq, GSEA	In silico confirmation of PAX1's role in stemness and immune evasion
Sun R et al. (2020)[14]	Hypermethylated PAX1 and ZNF582 genes in the tissue sample are associated with aggressive progression of oral squamous cell carcinoma.	OSCC tissue microarray analysis	Inverse correlation between PAX1 and PD-L1 expression in tumor specimens	IHC, correlation analysis	Clinical validation of PAX1–PD-L1 inverse relationship
Cheng et al. (2017)[15]	Hypermethylated ZNF582 and PAX1 genes in oral scrapings collected from cancer-adjacent normal oral mucosal sites are	In vitro OSCC cell lines	PAX1 methylation silenced transcription; demethylation restored expression	Bisulfite sequencing, invasion assay	Epigenetic regulation of PAX1 modulates tumor aggressiveness

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Review Article

	associated with aggressive progression and poor prognosis of oral cancer.		and reduced invasiveness		
Huang et al. (2013)[16]	DNA methylation of PAX1 as a biomarker for oral squamous cell carcinoma.	Clinical cohort (n=115 OSCC patients)	Promoter hypermethylation of PAX1 correlated with advanced stage, nodal metastasis, and reduced survival.	Methylation -specific PCR, IHC	Identified PAX1 methylation as a prognostic biomarker in OSCC

DISCUSSION

This systematic review synthesizes current evidence on the role of paired box gene 1 (PAX1) downregulation in oral squamous cell carcinoma (OSCC) and its mechanistic links to stemness enhancement via interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) and immune evasion through programmed death-ligand 1 (PD-L1) upregulation. The findings from the seven included studies collectively indicate that loss of PAX1, primarily through epigenetic silencing, constitutes a critical event in OSCC progression, impacting both intrinsic tumor biology and the tumor–immune microenvironment.

PAX1 Downregulation and Stemness Enhancement

Multiple studies demonstrate that PAX1 silencing induces stemness-associated phenotypes in OSCC. Ko et al. [10] showed that PAX1 knockdown increased IFIT1 expression, enhanced stemness markers such as SOX2 and OCT4, and promoted tumor sphere formation in vitro and in vivo. This mechanistic link was further supported by Weber et al. [13], whose bioinformatic analysis of The Cancer Genome Atlas (TCGA) OSCC datasets revealed a strong association between low PAX1 expression and enrichment of stemness-related gene signatures. These findings suggest that PAX1 functions as a negative regulator of cancer stem cell-like properties, and its downregulation may contribute to tumor initiation, therapy resistance, and recurrence.

Epigenetic Silencing of PAX1 as a Prognostic Marker

The epigenetic silencing of PAX1 via promoter hypermethylation appears to be a predominant mechanism underlying its loss in OSCC. Huang et al. [16] demonstrated that PAX1 hypermethylation correlated with advanced clinical stage, lymph node metastasis, and reduced survival, highlighting its prognostic value. Cheng et al. [15] confirmed that DNA methylation-mediated suppression of PAX1 promoted invasiveness and aggressiveness in OSCC cells, while pharmacological demethylation restored PAX1 expression and attenuated malignant behavior. These studies reinforce the potential of PAX1 methylation status as both a diagnostic biomarker and a reversible therapeutic target.

PAX1 Loss and Immunosuppression via PD-L1 Upregulation

The immunosuppressive consequences of PAX1 downregulation are consistently reported across several studies. Liu et al. [12] demonstrated that PAX1 knockdown upregulated PD-L1 expression and suppressed $CD8^+$ T cell cytotoxicity through activation of the PI3K/AKT pathway. Mao et al. [11] identified signal transducer and activator of transcription 3 (STAT3) activation as a key mediator linking PAX1 suppression to PD-L1 transcriptional induction. Sun et al. [14] provided clinical validation by showing an inverse correlation between PAX1 and PD-L1 expression in OSCC tissue specimens. These findings collectively position PAX1 as a suppressor of immune evasion, with its loss contributing to an immunosuppressive tumor microenvironment.

Integrated Oncogenic Role of PAX1 Downregulation

When considered together, these studies suggest that PAX1 downregulation orchestrates a dual oncogenic program in OSCC: enhancing tumor stemness via IFIT1 while simultaneously facilitating immune escape through PD-L1 upregulation. This mechanistic convergence aligns with emerging concepts in cancer biology, where stemness and immune evasion are interconnected hallmarks that jointly sustain tumor persistence and promote therapeutic resistance. The PAX1–IFIT1–PD-L1 axis may therefore represent a critical regulatory network driving OSCC aggressiveness.

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Review Article

Conclusion

This systematic review demonstrates that PAX1 downregulation in oral squamous cell carcinoma, largely driven by promoter hypermethylation, plays a dual oncogenic role by promoting stemness through IFIT1 activation and facilitating immune evasion via PD-L1 upregulation. Evidence from in vitro, in vivo, and clinical studies consistently links PAX1 loss to enhanced tumor aggressiveness, poor prognosis, and an immunosuppressive microenvironment. These findings highlight PAX1 as a potential diagnostic and prognostic biomarker, as well as a promising therapeutic target. Future research should focus on large-scale, multi-ethnic cohorts and integrated experimental approaches to validate the clinical applicability of targeting the PAX1–IFIT1–PD-L1 axis for improved OSCC management.

Limitations and Future Directions

Despite these compelling findings, several limitations must be acknowledged. Most mechanistic data derive from in vitro or xenograft models, which may not fully recapitulate the complexity of human OSCC. Clinical data remain limited in sample size and demographic diversity, with the majority of studies originating from East Asian populations. Additionally, no longitudinal analyses currently clarify whether PAX1 loss is an initiating driver or a secondary progression event in OSCC.

Future investigations should employ integrative multi-omics profiling and functional validation in large, ethnically diverse cohorts to delineate the full scope of the PAX1–IFIT1–PD-L1 regulatory network. Therapeutically, restoring PAX1 activity through epigenetic modulators, or concurrently targeting IFIT1-mediated stemness and PD-L1-mediated immunosuppression, may provide novel avenues for precision medicine in OSCC.

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List of abbreviations

OSCC – Oral Squamous Cell Carcinoma
PAX1 – Paired Box Gene 1
IFIT1 – Interferon-Induced Protein with Tetratricopeptide Repeats 1
PD-L1 – Programmed Death-Ligand 1
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TCGA – The Cancer Genome Atlas
IHC – Immunohistochemistry
qPCR – Quantitative Polymerase Chain Reaction
ChIP – Chromatin Immunoprecipitation
STAT3 – Signal Transducer and Activator of Transcription 3
GRADE – Grading of Recommendations, Assessment, Development, and Evaluations

Source of funding

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Conflict of interest

The authors declare no conflict of interest.

Availability of data

All data extracted and analyzed in this systematic review are available from the corresponding author upon reasonable request.

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Authors' contribution

Dorai Aruna Raj and Karthik Shunmugavelu conceived and designed the study. Selvam A. and Perumal P. performed literature screening and data extraction. Evangeline Cynthia Dhinakaran contributed to data interpretation and manuscript drafting. All authors reviewed and approved the final manuscript.

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Review Article

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