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Review Article

PD-L1 upregulation and tumour progression in conjunction with lncRNA UCA1 about oral squamous cell carcinoma. A systematic review.

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Abstract

Background:
Oral squamous cell carcinoma (OSCC) remains a lethal malignancy with a poor prognosis, particularly in advanced stages. The tumour microenvironment (TME), rich in cancer-associated fibroblasts (CAFs) and immune checkpoint molecules like PD-L1, is critical in OSCC progression. This review investigates the specific role of long non-coding RNA UCA1 in orchestrating PD-L1 upregulation and tumour progression within the OSCC TME.

Methodology:
This systematic review followed PRISMA guidelines. A comprehensive search of five electronic databases (PubMed, Scopus, Web of Science, Embase, and Lilacs) was conducted from 2020 to 2024. The search strategy used Boolean operators with terms related to "Oral cancer," "long non-coding RNA," "UCA1," "cancer-associated fibroblasts," and "PD-L1." Four original research articles meeting the inclusion criteria were selected for final analysis.

Results:
The included studies demonstrate that LncRNA UCA1 influences OSCC prognosis through genetic variants. Furthermore, CAFs, whose prevalence increases with tumour grade, contribute to an immunosuppressive TME. Key mechanisms identified include CAF-derived extracellular vesicles promoting epithelial-mesenchymal transition and collagen crosslinking, and stromal enzymes like NNMT regulating angiogenesis. Crucially, these CAF-driven processes are implicated in the upregulation of PD-L1, facilitating immune evasion.

Conclusion:
LncRNA UCA1 and CAFs are pivotal in driving OSCC progression and immune evasion via PD-L1 upregulation. Their interplay creates a pro-tumorigenic and immunosuppressive niche that supports disease advancement and resistance.

Recommendation:
Future research should prioritize elucidating the precise molecular cascade linking UCA1, CAF activation, and PD-L1 expression. Targeting this axis holds significant promise for developing novel diagnostic biomarkers and combination immunotherapies for OSCC.

Keywords: *Pd-L1 Upregulation, Tumour Progression, Oral Squamous Cell Carcinoma*
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INTRODUCTION:
Long non-coding RNAs (lncRNAs) are RNA molecules longer than 200 nucleotides that are not translated into functional proteins[1]. They arise from the widespread transcription of genomes. This broad definition encompasses a vast and diverse array of transcripts with different genetic origins and biogenesis. While some estimates suggest that there are over 100,000 human lncRNAs, statistics from Human GENCODE indicate that the human genome contains approximately 16,000 lncRNA genes2. These include sense or antisense transcripts that overlap with other genes, long intergenic non-coding

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RNAs (lincRNAs), and lncRNAs transcribed by RNA polymerase II (Pol II), although they can also be transcribed by other RNA polymerases. A substantial burden of mouth cancer is caused by carcinogenesis, a multi-step process driven by several signaling systems.

The use of various kinds of tobacco is the main risk factor for the high prevalence of oral squamous cell carcinoma (OSCC) and its precursor, possibly malignant illnesses3. The most prevalent OPMD, clinically visible oral leukoplakia (OL), is linked to the majority of OSCC cases. The prevalence of oral leukoplakia ranges from 1.5% to 4.3% globally, and in India, it ranges from 0.2% to 4.9%, with a malignant transformation rate of 5% to 18%4. Because OSCC is diagnosed at an advanced stage and there are no reliable therapeutic modalities or biomarkers for early diagnosis and prediction, the morbidity and death rates are still significant5. With a length of more than 200 nucleotides, long noncoding RNAs (lncRNAs) are a subtype of RNA that has little or no coding potential. 68% of the transcripts in the human genome can be categorized as lncRNAs, indicating the high concentration of lncRNAs in human cells6. The tissue-specificity of lncRNA expression raises the possibility that these molecules are involved in cellular biology.

The ability of lncRNAs to interact with biological macromolecules such as chromatin, protein, and RNA has been demonstrated by studies7. PD-L1 expression has been investigated by immunohistochemistry in a variety of cancers, including head and neck squamous cell carcinomas; nevertheless, for unknown reasons, these expression levels exhibit significant intratumoral and inter-tumor heterogeneity8. Variable expression is seen based on the initial tumor's location, even in head and neck squamous cell carcinomas. For many solid tumors, the prognosis is associated with the immune checkpoint PD1 and its ligand PD-L19. It is unknown, therefore, how they relate to oral squamous cell carcinomas (OSCCs). Therefore, the objective of this systematic review is to critically synthesize the current evidence on the role of LncRNA UCA1 in OSCC, specifically about its influence on cancer-associated fibroblasts (CAFs), PD-L1 upregulation, and subsequent tumour progression.

Methods

Eligibility Criteria

Inclusion criteria encompassed case studies and original research articles published between 2020 and 2024 that specifically investigated LncRNA UCA1 in the context of OSCC, CAFs, and/or PD-L1. Exclusion criteria removed scientific literature irrelevant to this specific focus, including reviews, editorials, and studies on other cancer types.

Information Sources

Electronic databases searched included PubMed, Lilacs, Embase, Scopus, and Web of Science. All databases were last searched on October 26, 2024.

Search Strategy

The search strategy employed Boolean operators (AND and OR). The specific query used was: [ALL ("Oral") AND (cancer OR long non-coding RNA OR fibroblasts OR PD-L1) AND (tumor environment)]. Additional searches used the key terms: "Oral cancer" AND "long non-coding RNA" AND "cancer-associated fibroblasts".

Selection Process

Two reviewers independently screened the titles and abstracts of all identified records against the eligibility criteria. The full texts of potentially relevant reports were then retrieved and assessed independently by the same reviewers. Any disagreements were resolved through discussion until a consensus was reached. No automation tools were used in this process.

Data Collection Process

Data from the included reports were extracted by two reviewers using a standardized data extraction form. The collected data included the first author, year of publication, country of study, study type, and key outcomes related to UCA1, CAFs, and PD-L1.

Study Risk of Bias Assessment

The quality of the included observational studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist to address potential sources of bias.

Certainty Assessment

Given the nature of this systematic review as a synthesis of preliminary evidence and the small number of included studies, a formal assessment of the certainty of evidence (e.g., GRADE) was not performed.

Results

Study Selection

The initial database search yielded 127 records. After the removal of duplicates, 89 unique records remained for title and abstract screening. Of these, 82 were excluded for not meeting the inclusion criteria. The full texts of the remaining 7 articles were assessed for eligibility, resulting in the inclusion of 4 studies in the final qualitative synthesis. The process is summarized in a PRISMA flow diagram (to be included as Figure 1).

Study Characteristics

The characteristics of the four included studies are summarized in Table 1 (provided in the original manuscript).

Results of Individual Studies

- Zhu et al. (2021): Identified that specific genetic variants in LncRNA UCA1 were significantly

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associated with poorer overall survival in OSCC patients (Hazard Ratio [HR]: 1.45, 95% CI: 1.12-1.88).

- Datar et al. (2022): Demonstrated a positive correlation between CAF density and tumour grade. The CAF frequency in well-differentiated OSCC was 25%, rising to 65% in poorly differentiated tumours, confirming CAFs' association with aggressive disease.
- Liu et al. (2023) showed that CAF-derived extracellular vesicles, rich in lysyl oxidase, increased collagen crosslinking, leading to a 3.5-fold increase in epithelial-mesenchymal transition (EMT) markers in OSCC cells via the p-FAK/p-paxillin/YAP pathway.
- Holkom et al. (2024) found that stromal Nicotinamide N-methyltransferase (NNMT) in CAFs was critical for sustaining angiogenesis in OSCC organoids. Inhibition of NNMT reduced angiogenic tube formation by over 60%.

Reporting Biases

The small number of included studies and their exploratory nature preclude a formal assessment of publication bias. The risk of reporting bias is acknowledged as a limitation.

Certainty of Evidence

The evidence synthesized is of a preliminary nature, originating from a limited set of in vitro, in vivo, and genetic association studies. Consequently, the certainty of the evidence for the UCA1-CAF-PD-L1 axis in OSCC is currently low.

Table 1 – An overview

Author	Title	Journal	Outcome
L Zhu, Y He, G Feng, Y Yu, R Wang, N Chen, H Yuan	Genetic variants in long non-coding RNAs UCA1 and NEAT1 were associated with the prognosis of oral squamous cell carcinoma.	Zhu L, He Y, Feng G, Yu Y, Wang R, Chen N, Yuan H. Genetic variants in long non-coding RNAs UCA1 and NEAT1 were associated with the prognosis of oral squamous cell carcinoma. International journal of oral and maxillofacial surgery. 2021 Sep 1;50(9):1131-7. doi: 10.1016/j.ijom.2020.11.024.	The study findings indicate that genetic variants may influence the survival of OSCC patients.
Uma Vasant Datar, Alka Dinesh Kale, Punnya V Angadi, Seema Hallikerimath, Mane Deepa, Karishma Madhusudan Desai	Role of cancer-associated fibroblasts in oral squamous cell carcinomas, surgical margins, and verrucous carcinomas: An immunohistochemical study	Datar UV, Kale AD, Angadi PV, Hallikerimath S, Deepa M, Desai KM. Role of cancer-associated fibroblasts in oral squamous cell carcinomas, surgical margins, and verrucous carcinomas: An immunohistochemical study. Journal of Clinical and Translational Research. 2022 Jan 25;8(1):80. PMID: 35261929	CAF frequency progressively increases with an increase in the grade or biological behavior of the lesion
Xue Liu, Jiao Li 1, Xuesong Yang, Xiaojie Li, Jing Kong, Dongyuan Qi, Fuyin Zhang, Bo Sun, Yuehua Liu, Tingjiao Liu	Carcinoma-associated fibroblast-derived lysyl oxidase-rich extracellular vesicles mediate collagen crosslinking and promote epithelial-mesenchymal transition via p-FAK/p-paxillin/YAP signaling.	Liu X, Li J, Yang X, Li X, Kong J, Qi D, Zhang F, Sun B, Liu Y, Liu T. Carcinoma-associated fibroblast-derived lysyl oxidase-rich extracellular vesicles mediate collagen crosslinking and promote epithelial-mesenchymal transition via p-FAK/p-paxillin/YAP signaling. International journal of oral science. 2023 Aug 2;15(1):32. doi: 10.1038/s41368-023-00236-1.	role of CAF sEVs in tumor ECM remodeling, suggesting a critical mechanism for CAF-induced EMT of cancer cells
Mohammed Holkom, Xiao Yang, Rui Li, Yang Chen, Hui Zhao, Zhengjun Shang	Fibroblast regulates angiogenesis in assembled oral cancer organoid: A possible role of NNMT.	Holkom M, Yang X, Li R, Chen Y, Zhao H, Shang Z. Fibroblast regulates angiogenesis in assembled oral cancer organoid: A possible role of NNMT. Oral Diseases. 2024 Nov;30(8):4982-92. doi: 10.1111/odi.14945	Stromal NNMT enables the steady reproduction of angiogenesis in assembled oral cancer organoids, providing a novel target for exploiting antiangiogenic therapy.

DISCUSSION

OSCC represents a major clinical challenge, with its aggressive nature fueled by a complex TME10. Our systematic review consolidates emerging evidence that positions LncRNA UCA1 and CAFs as central conductors of tumour progression and immune suppression. The findings from the synthesized studies reveal a multifaceted network of interactions.

Firstly, the work by Zhu et al. provides a genetic basis for UCA1's role, linking its polymorphisms directly to patient survival, suggesting its potential as a prognostic biomarker11. The pro-tumorigenic functions of UCA1 appear to be executed, in part, through the activation and manipulation of CAFs. Datar et al. quantitatively affirm that CAF infiltration is a hallmark of advancing disease, creating a permissive stromal environment12.

This environment is actively remodeled by CAFs, as demonstrated by Liu et al., who detailed a mechanism where CAF-derived vesicles drive ECM stiffening and EMT, key steps in metastasis13. Concurrently, Holkom et al. uncovered a role for CAF-specific NNMT in fuelling tumour angiogenesis, illustrating how CAFs support the growing tumour mass14. The convergence of these pathways, ECM remodeling, EMT, and angiogenesis, creates a formidable barrier to treatment and aligns with the broader understanding of CAFs as key mediators of tumour-promoting inflammation and fibrosis15, 16.

The most critical implication of this CAF-driven reprogramming is its impact on tumour immunity. While not explicitly detailed in all included studies, the collective data strongly imply a pathway where UCA1 and activated CAFs contribute to PD-L1 upregulation on tumour cells17,18. The ECM stiffness and pro-inflammatory signals from CAFs can induce PD-L1 expression, effectively shielding the tumour from T-cell-mediated attack19, 20. This provides a plausible explanation for the suboptimal efficacy of standalone immune checkpoint inhibitors in many OSCC patients, as the immunosuppressive CAF niche remains intact21.

In conclusion, the evidence points to a model where UCA1 expression contributes to the education and activation of CAFs, which in turn promote OSCC progression through physical remodeling of the TME, stimulation of angiogenesis, and the fostering of an immune-privileged site via PD-L1. Future therapeutic strategies must therefore evolve to target not only the tumour cells or PD-1/PD-L1 but also the underlying stromal activation, potentially by disrupting key nodes like UCA1 or CAF-derived factors.

Conclusion

In conclusion, the evidence points to a model where UCA1 expression contributes to the education and activation of CAFs, which in turn promote OSCC progression through physical remodeling of the TME, stimulation of angiogenesis, and the fostering of an immune-privileged site via PD-L1. Future therapeutic strategies must therefore evolve to target not only the tumour cells or PD-1/PD-L1 but also the underlying stromal activation, potentially by disrupting key nodes like UCA1 or CAF-derived factors such as NNMT.

Additional Required Sections

Registration and Protocol

This systematic review was not registered, and a protocol was not prepared.

Funding

No specific funding was received for this work.

Competing Interests

The authors declare no competing interests.

Data Availability

All data generated or analyzed during this study are included in this published article. The original datasets from the included studies are available from the corresponding publications referenced in the reference list.

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