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Research Article

Exosomal microRNA signatures in the crossroads of periodontitis and HNSCC

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Abstract

Introduction: Inflammatory pathways are considered the crossroads of oral cancer and periodontitis. Exosomal microRNAs (miRNAs) have emerged as key regulators linking inflammation and carcinogenesis.

Aim: This study aimed to identify differentially expressed miRNAs associated with periodontitis (PD) and evaluate their relevance in head and neck squamous cell carcinoma (HNSCC) using a bioinformatics approach.

Materials and methods: miRNA expression data from the GSE89081 dataset (n=10) were analyzed using GEO2R with an adjusted p-value of <0.05. Selected miRNAs were validated in the TCGA-HNSCC dataset via UALCAN, followed by survival analysis. Exosomal localization and target gene prediction were performed using ExoCarta and TargetScan.

Results: Among the 25 microRNAs curated from the dataset based on statistical significance, five were significantly expressed in HNSCC and had a notable impact on patient survival. A set of differentially expressed miRNAs was identified, among which hsa-miR-193b-5p and hsa-miR-877-5p were consistently upregulated in both PD and HNSCC datasets. Higher expression levels of these miRNAs were associated with reduced overall survival.

Conclusions: The microRNAs, hsa-miR-193b-5p, and hsa-miR-877-5p were significantly upregulated in both datasets. Also, overexpression of these microRNAs was associated with reduced overall survival in patients with HNSCC. Furthermore, low expression of the target transcript of hsa-miR-193b-5p, *FLI1,* was associated with poor survival in HNSCC patients. These findings suggest a potential role in inflammation-associated carcinogenesis; however, due to the small sample size and *in silico* design, further experimental validation is warranted.

Keywords

cancer, diseases, gene expression, genetics, microRNA, periodontitis, survival

Introduction

Emerging evidence links periodontitis (PD) and head and neck squamous cell carcinoma (HNSCC) as significant global health burdens, underscoring a complex dimension of their correlation.[1] The prevalence of periodontitis may reach up to 90% of the world's population at some point in life, leading to both connective tissue and bone destruction, significantly contributing to the loss of teeth in adults. Concurrently, HNSCC is a prevalent cancer affecting the oral cavity, pharynx, and larynx. It is closely related to risk factors like tobacco, alcohol, and human papillomavirus (HPV) infection.[2] Recent reports suggest that periodontitis may be a risk factor for HNSCC, mediated by sustained inflammation, oxidative stress, and carcinogenic microbial agents.[3] The mechanistic link between PD and HNSCC is heavily driven by sustained, localized chronic inflamma-

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tion rather than a generalized inflammatory process.[4]

Chronic inflammatory processes, the microbiome, and immune modulation have been identified as common hallmarks for both conditions, suggesting a probable bidirectional relationship between the two. It involves the chronic inflammatory process in which a series of complicated interactions occur between microbial and host factors. Common biomarkers, such as IL-6, IL-8, TNF-α, and MMPs, are present in both instances, augmenting inflammation and tissue remodeling, indicating a common pathway, not only targeted for therapeutic intervention.[5] Host responses to microbial infection activate inflammatory pathways, and dysregulation of these processes can lead to chronic inflammation and tissue damage. Pathogens such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum, Tannerella forsythia,* and *Treponema denticola* are a few highly virulent periodontic pathogens with virulence factors that affect the host cell signaling pathway (e.g., PI3K/Akt, Wnt/β-catenin), ultimately creating a microenvironment conducive to tumor progression. Certain other lifestyle factors exacerbate the effects of both periodontitis and HNSCC by increasing oxidative damage and diminishing immune surveillance.[6,7] Additional factors, including the epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, play a key role in regulating gene expression and are closely associated with tumor-promoting inflammation.[8,9]

Exosomal miRNA (ExomiR) has emerged as a potential marker in cancer and inflammatory diseases.[10] Exosomes produced by malignant cells can facilitate the transfer of these altered miRNAs, which can then be passed on to nearby or distant cells, thereby promoting tumor growth and metastasis.[11] In periodontitis, exosomal miRNAs are involved in the immune response, osteoclastogenesis, and tissue remodeling, whereas in HNSCC, they are implicated in tumor proliferation, angiogenesis, metastasis, and immune evasion. miRNA signatures, such as miR-21, miR-155, and miR-146a, may provide a possible link between chronic periodontal inflammation and carcinogenesis, shedding light on potential shared pathways and associations.[12] While previous studies have established the independent roles of microRNAs in both periodontitis and oral cancers, they present with notable limitations. The exact molecular crosstalk that mediates the transition from a localized chronic inflammatory state to a malignant phenotype remains largely unknown.

Aim

As a means to address this gap, the present study was designed using a computational approach to decipher the role of common microRNAs expressed in both disease conditions, with a special emphasis on exosomal microRNAs. By elucidating the common molecular pathways and targeting shared transcripts, this study aims to unravel the complex crosstalk between periodontal inflammation and carcinogenesis.

Materials and methods

Study dataset

The microRNA expression profile was retrieved from the GSE89081 dataset[13] hosted on the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo). The dataset consisted of microRNA profiles from five healthy subjects (N) and five patients with periodontitis (PD). The quantitative PCR assays assessed the microRNAs expressed exclusively in the gingival crevicular fluid. Differentially expressed microRNAs were identified using the GEO2R tool.[14]

MicroRNA expression analysis

The hub of microRNAs identified in GSE89081 was further assessed for gene expression in the HNSCC dataset (TCGA) using UALCAN.[15] Differential expression analysis was performed using GEO2R with thresholds set at an adjusted p-value of <0.05, and the log2 fold change threshold was set at 0. The Benjamini and Hochberg (false discovery rate) was applied. The significant differences in expression levels between normal and primary tumors were estimated using Welch's t-test.

Kaplan–Meier survival analysis

It is an important criterion for prognostic validation of the microRNA of interest. Kaplan-Meier analyses used to analyse overall survival based on patient's expression profile. The samples with expression values above the third quartile were designated as the high expression group, and samples with gene expression values below the third quartile were defined as low/medium expression groups. The R packages "survival" and "survminer" generated the survival plots. The log-rank tests determined the p values, indicating the significance level.[16]

Statistical analysis

Gene expression data from multiple datasets were thoroughly examined using the robust GEO2R tool to present findings in detailed tables and graphical plots. The UALCAN portal performed an extensive analysis of gene expression profiles by comparing expression levels across groups through a PERL script supported by the Comprehensive Perl Archive Network (CPAN) module. Furthermore, survival plots were created using the "survival" and "survminer" R packages, and the plots were compared using the log-rank test. The "survival" package was used for detailed survival analysis, which included survival curves, hypothesis tests, and models. In contrast, the "survminer"

package notably improved the visualization of Kaplan–Meier and forest plots, promoting clear and comprehensive interpretation of complex survival data.[14,16]

Exosomal location analysis

The ExoCarta (http://www.exocarta.org), a web-based repository of manually curated exosomal RNA, proteins, and lipids, was used to identify the exosomal localization of microRNAs. ExoCarta hosts over 119,000 entries, with tools to explore the protein-protein interaction networks and biological pathways that are essential for downstream computational analysis. The differentially expressed microRNAs, sorted based on similar expression profiles in both datasets and the survival status of HNSCC patients, were further analyzed to demonstrate their exosomal localization.[17]

Target identification

TargetScan is a well-known bioinformatics tool for predicting miRNA targets across different organisms. It predicts probable miRNA binding sites by searching for conserved 8-mer, 7-mer, and 6-mer seed matches within the 3‘ UTRs of mRNAs. TargetScan considers evolutionary conservation, site context scores, and other features, such as local AU content and site accessibility, to improve prediction accuracy. By integrating these parameters, TargetScan assists researchers in understanding post-transcriptional gene regulation and in prioritizing functionally relevant miRNA-mRNA interactions. It thus finds applications in various studies of gene expression networks, cancer biology, and complex genetic disorders, where miRNA dysregulation plays a significant role.[18,19]

Results

Differential expression of MicroRNA in periodontitis

The GSE89081 dataset showed 21 upregulated and 4 downregulated microRNAs, sorted by adjusted *p*-values of <0.05 **(Fig. 1, Table 1)**. A significant majority of the upregulated microRNAs demonstrated positive log2 fold changes up to roughly 1.98. Conversely, a smaller subset, such as hsa-miR-1256 and hsa-miR-1181, is downregulated, marked by negative values. The adjusted p-values indicate strong statistical significance, with most values tightly clustered at 0.0351, highlighting a robust set of expression variations.

Validation in HNSCC dataset

Among the 25 microRNAs, three microRNAs, hsa-miR-187-3p, hsa-miR-200a-5p, and hsa-miR-222-5p, were found to show a similar expression pattern in both PD and HNSCC groups. The upregulation of these microRNAs correlated with better overall survival**.** Additionally, two other microRNAs, hsa-miR-193b-5p and hsa-miR-877-5p, were also found to exhibit the same kind of expression profile, demonstrating its association with reduced overall survival **(Fig. 2, Table 2)**.

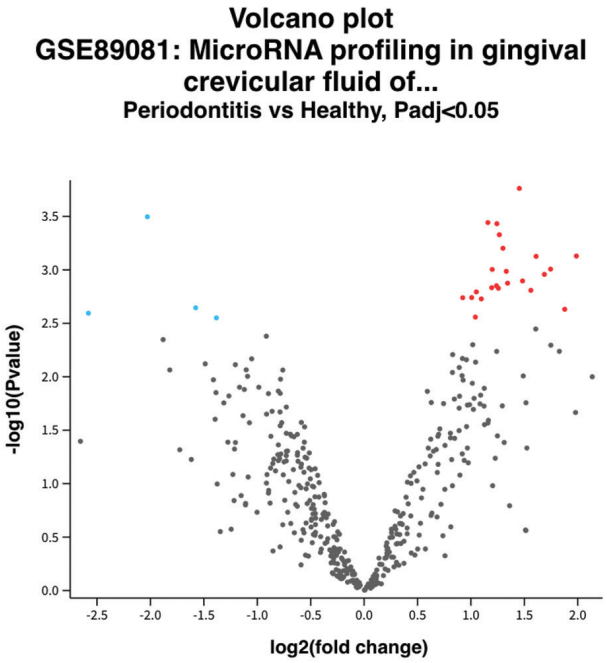

Figure 1. Volcano plot demonstrating the differentially expressed microRNAs in the PD group when compared to normal healthy subjects.

Survival analysis

The Kaplan–Meier survival analysis revealed that higher hsa-miR-193b-5p expression was associated with poor overall survival, with a hazard ratio of 1.38 (95% CI: 1.01–1.88), indicating a 38% increased risk of death in the high-expression group. The log-rank p-value of 0.045 suggests a strong, statistically significant association. On the other hand, hsa-miR-877-5p expression was consistently higher in periodontitis than in the healthy group. The hazard ratio of 1.39 (95% CI: 1.06–1.82) indicated a 39% higher risk of death in HNSCC patients with high expression of hsa-miR-877-5p. The log-rank test (p=0.018) confirms the statistical significance of this observation.

Exosomal location

The differentially expressed microRNAs with prognostic significance were analyzed using ExoCarta. The hsa-miR-187-3p, miR-200a-5p, and hsa-miR-222-5p were found to be located within the colorectal cancer cell-derived small extracellular vesicles, whereas hsa-miR-193b-5p was reported to be present in the plasma cell-derived vesicles. In contrast, hsa-miR-877-5p has not yet been documented in

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Table 1. The list of differentially expressed microRNAs (DEMs) identified in the GCF of PD patients when compared to healthy periodontium

Differentially expressed miRNA	Log 2 fold change	Gene expression	Adjusted *p* value
hsa-miR-152-3p	1.45282	Upregulated	0.0351
hsa-miR-1256	−2.02846	Downregulated	0.0351
hsa-miR-22-3p	1.15882	Upregulated	0.0351
hsa-miR-187-3p	1.24282	Upregulated	0.0351
hsa-miR-200c-5p	1.26554	Upregulated	0.0351
hsa-miR-200a-5p	1.29954	Upregulated	0.0351
hsa-miR-30b-3p	1.98682	Upregulated	0.0351
hsa-miR-193b-5p/3p	1.60954	Upregulated	0.0351
hsa-miR-27b-5p	1.74554	Upregulated	0.0351
hsa-miR-181b-5p	1.19882	Upregulated	0.0351
hsa-miR-151a-5p/3p	1.33082	Upregulated	0.0351
hsa-miR-222-5p	1.68754	Upregulated	0.0351
hsa-miR-99b-5p/3p	1.34282	Upregulated	0.0351
hsa-miR-31-3p	1.19482	Upregulated	0.0351
hsa-miR-21-3p	1.25682	Upregulated	0.0351
hsa-miR-455-5p	1.56082	Upregulated	0.0351
hsa-miR-34c-5p	1.05082	Upregulated	0.0351
hsa-miR-877-5p	0.92282	Upregulated	0.0353
hsa-miR-671-5p	1.09682	Upregulated	0.0353
hsa-miR-194-3p	−1.57646	Downregulated	0.0404
hsa-miR-125b-1-3p	1.87754	Upregulated	0.0404
hsa-miR-1181	−2.58046	Downregulated	0.0422
hsa-miR-200b-5p	1.04154	Upregulated	0.0432
hsa-miR-582-3p	−1.38246	Downregulated	0.0432
hsa-miR-100-5p	1.60682	Upregulated	0.053

the vesicles. The presence of these microRNAs in exosomes makes them a potential source of diagnostic and prognostic biomarkers, as they are safely encapsulated within the vesicles, preventing rapid degradation.

Target analysis

The analysis of potential targets of the curated microRNAs using TargetScan revealed 21, 3225, 286, 4365, 3859, and 131 transcripts for hsa-miR-187-3p, hsa-miR-200a-5p, hsa-miR-193b-3p, hsa-miR-193b-5p, hsa-miR-222-5p, and hsa-miR-877-5p, respectively. The top 5 transcripts for each microRNA were further assessed for their expression in the TCGA HNSCC dataset. Among the 30 target transcripts, six, *NRG2, BARX2, CWH43, UPRT, SPINK8,* and *TP53INP2*, were found to be downregulated. Although none of these transcripts influenced the patient's overall survival, one observation was made with the *FLI1* gene transcript, which demonstrated overexpression in tumor tissues. Interestingly, low *FLI1* transcript expression correlated with reduced overall survival in HNSCC patients **(Fig. 3, Table 3)**.

Discussion

MicroRNAs are key post-transcriptional regulators involved in inflammation and cancer, and their dysregulation contributes to various human diseases, including cardiovascular, metabolic, and malignant disorders, particularly in both periodontitis and HNSCC.[20-23] In this study, a total of 25 differentially expressed microRNAs were identified in periodontitis, among which hsa-miR-193b-5p and hsa-miR-877-5p showed consistent upregulation in both PD and HNSCC datasets. Notably, higher expression levels of these miRNAs were associated with reduced overall survival in HNSCC patients, suggesting their potential involvement in inflammation-associated carcinogenesis. Previous studies have also highlighted the role of dysregulated miRNAs in HNSCC. For instance, Anees et al. reported altered expression of miR-7-3p in association with STAT3 signaling, while Varshan et al. demonstrated the involvement of miR-34a-3p in TNF-α-mediated inflammatory pathways in oral cancer.[24,25] These findings collectively support the role of miRNA-mediated regulatory networks in linking inflammation and tumorigenesis.

Table 2. The gene expression profile of DEGs curated from the PD group analyzed in the HNSCC (TCGA dataset) and their survival analysis

miRNA	Gene expression in PD	Gene expression in HNSCC	*P*-value	Survival analysis	Prognosis in HNSCC patients
hsa-miR-152-3p	Upregulated	Downregulated	2.43×10^{-2}	0.0065	Good
hsa-miR-1256	Downregulated	Upregulated	2.43×10^{-4}	0.0056	Poor
hsa-miR-22-3p	Upregulated	Insignificant	4.77×10^{-1}	0.0041	Poor
hsa-miR-187-3p	**Upregulated**	**Upregulated**	$\mathbf{7.09\times10^{-11}}$	**0.054**	**Good**
hsa-miR-200c-5p	Upregulated	Upregulated	2.72×10^{-6}	0.23	Insignificant
hsa-miR-200a-5p	**Upregulated**	**Upregulated**	$\mathbf{9.82\times10^{-4}}$	**0.0047**	**Good**
hsa-miR-30b-3p	Upregulated	Downregulated	1.08×10^{-2}	0.027	Poor
hsa-miR-193b (5p/3p)	**Upregulated**	**Upregulated**	$\mathbf{1.62\times10^{-12}}$	**0.045**	**Poor**
hsa-miR-27b-5p	Upregulated	Downregulated	1.18×10^{-9}	0.086	Insignificant
hsa-miR-181b-5p	Upregulated	Upregulated	8.36×10^{-10}	0.096	Insignificant
hsa-miR-151a-5p/3p	Upregulated	Downregulated	1.69×10^{-3}	0.03	Good
hsa-miR-222-5p	**Upregulated**	**Upregulated**	$\mathbf{8.44\times10^{-8}}$	**0.022**	**Good**
hsa-miR-99b (5p/3p)	Upregulated	Upregulated	4.73×10^{-13}	0.2	Insignificant
hsa-miR-31-3p	Upregulated	Upregulated	$<10^{-12}$	0.18	Insignificant
hsa-miR-21-3p	Upregulated	Upregulated	1.62×10^{-12}	0.13	Insignificant
hsa-miR-455-5p	Upregulated	Upregulated	$<10^{-12}$	0.17	Insignificant
hsa-miR-34c-5p	Upregulated	Insignificant	2.58×10^{-1}	0.2	Insignificant
hsa-miR-877-5p	**Upregulated**	**Upregulated**	$\mathbf{1.62\times10^{-12}}$	**0.018**	**Poor**
hsa-miR-671-5p	Upregulated	Upregulated	1.62×10^{-12}	0.085	Insignificant
hsa-miR-194-3p	Downregulated	Upregulated	2.15×10^{-3}	0.16	Insignificant
hsa-miR-125b-1-3p	Upregulated	Downregulated	2.04×10^{-9}	0.0094	Poor
hsa-miR-1181	Downregulated	Upregulated	7.17×10^{-3}	0.024	Poor
hsa-miR-200b-5p	Upregulated	Insignificant	6.30×10^{-1}	0.0088	Low-Poor
hsa-miR-582-3p	Downregulated	Insignificant	9.22×10^{-1}	0.43	Insignificant
hsa-miR-100-5p	Upregulated	Downregulated	1.11×10^{-16}	0.00056	Good

In the present study, five microRNAs demonstrated consistent expression patterns across both datasets, with hsa-miR-193b-5p and hsa-miR-877-5p being associated with reduced overall survival. Their upregulation in periodontitis suggests a role in inflammatory processes and tissue destruction, while their elevated expression in HNSCC supports their potential involvement in tumor progression. The consistent expression of these miRNAs across both conditions indicates a possible shared molecular pathway underlying inflammation-driven carcinogenesis. These findings suggest that hsa-miR-193b-5p and hsa-miR-877-5p may serve as potential biomarkers for disease progression and prognosis. Furthermore, the identification of hsa-miR-193b-5p in exosomal datasets highlights its potential relevance in non-invasive biomarker development, although this requires further validation.

Chronic inflammation is a key feature linking periodontitis and cancer progression. A study by Xie et al. demonstrated distinct microRNA expression profiles in inflamed gingival tissues compared to healthy controls, highlighting the involvement of miRNAs in periodontal inflammation and disease pathogenesis. Their findings identified several dysregulated miRNAs associated with immune and inflammatory pathways, supporting the role of miRNAs as potential molecular markers in periodontitis.[26]

Previous studies have reported miR-193b-5p as a context-dependent regulator in various cancers, often associated with tumor progression. Dinami et al. demonstrated that miR-193b-5p contributes to colorectal cancer development through regulation of tumor-suppressive pathways.[27] Similarly, reduced expression of miR-193b-5p has been associated with improved survival outcomes in pleural mesothelioma, supporting its potential oncogenic role.[28] In glioma, increased miR-193b-5p expression has been linked to enhanced tumor proliferation, migration, and poor overall survival.[29] These findings are consistent with our observations, where hsa-miR-193b-5p was upregulated and associated with reduced overall survival in HNSCC, suggesting its potential involvement in inflammation-driven carcinogenesis.

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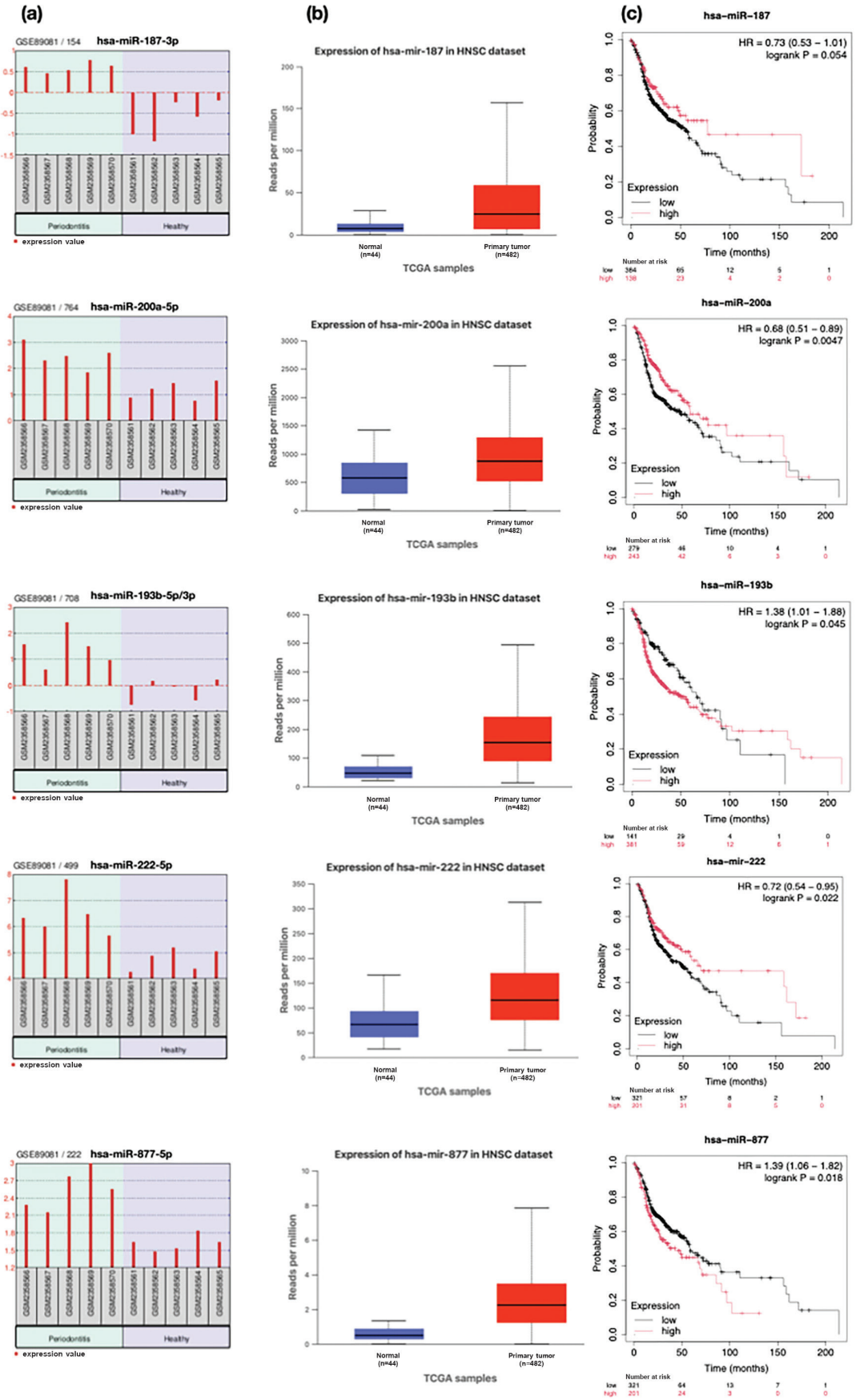

Figure 2. (**a**) Bar graph demonstrating the expression profile of microRNAs in the periodontitis group; (**b**) Box-whisker plot demonstrating the expression of microRNAs in HNSCC patients; (**c**) The overall survival of HNSCC patients as assessed using the Kaplan–Meier survival plotter.

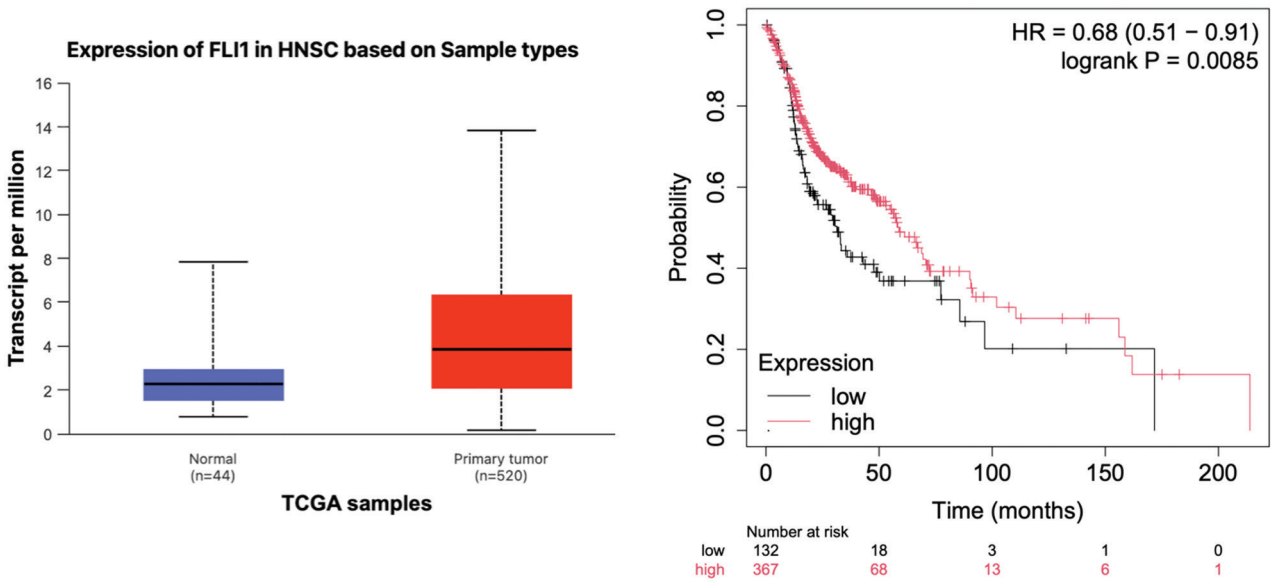

Figure 3. (**a**) Box-whisker plot demonstrating the overexpression of *FLI1* gene in primary tumor tissue of HNSCC patients (*p*-value = 4.95×10^{-3}), (b) Kaplan–Meier survival plot demonstrates the low expression of *FLI1* transcript leading to poor overall survival of head and neck cancer patients (*p*-value = 0.0085).

Table 3. Top 5 target genes of the curated set of microRNAs

microRNA	Target gene	Gene expression in HNSCC	*p*-value	Survival	*p*-value
hsa-miR-187-3p	*LRFN1*	Upregulated	$<10^{-12}$	Insignificant	0.45
	CRMP1	Upregulated	9.01×10^{-9}	Insignificant	0.81
	NRG2	**Downregulated**	2.02×10^{-5}	Insignificant	0.46
	BARX2	**Downregulated**	3.58×10^{-12}	Insignificant	0.96
	FGF9	Insignificant	5.05×10^{-1}	Insignificant	0.52
hsa-miR-200a-5p	*ZNF99*	Insignificant	6.37×10^{-1}	NA	NA
	LSM 6	Upregulated	1.62×10^{-12}	Insignificant	0.93
	ASNSD1	Upregulated	1.78×10^{-4}	Insignificant	0.62
	CWH43	**Downregulated**	3.77×10^{-2}	Insignificant	0.31
	SFRS7	Upregulated	4.29×10^{-10}	Insignificant	0.088
hsa-miR-193b-3p	*ARL8B*	Upregulated	1.56×10^{-5}	Insignificant	0.77
	ZNF791	Upregulated	4.05×10^{-3}	High - Good prognosis	0.0085
	SLC14A1	Insignificant	1.16×10^{-1}	Insignificant	0.061
	C15ORF40	Upregulated	1.68×10^{-5}	Insignificant	0.54
hsa-miR-193b-5p	*SLC10A6*	Insignificant	1.90×10^{-1}	Insignificant	0.32
	IL17RD	Insignificant	1.05×10^{-1}	Insignificant	0.5
	FLI1	**Upregulated**	$\mathbf{4.95\times10^{-3}}$	Low - Poor prognosis	**0.031**
	SLC39A5	Upregulated	5.22×10^{-7}	Insignificant	0.067
	C11ORF51	Upregulated	3.99×10^{-15}	Insignificant	0.59
hsa-miR-222-5p	*WFDC8*	Insignificant	6.46×10^{-1}	NA	NA
	ZP1	Insignificant	1.58×10^{-1}	Insignificant	0.29
	UPRT	**Downregulated**	7.04×10^{-4}	Insignificant	0.32
	SPINK8	**Downregulated**	4.82×10^{-4}	NA	NA
	APOH	Insignificant	9.01×10^{-1}	NA	NA
hsa-miR-877-5p	*ZNF174*	Upregulated	1.62×10^{-12}	Insignificant	0.48
	TP53INP2	**Downregulated**	1.42×10^{-4}	Insignificant	0.97
	TMCC2	Upregulated	2.37×10^{-9}	Insignificant	0.48
	PDPN	Upregulated	$<10^{-12}$	Insignificant	0.13
	FOXM1	Upregulated	1.62×10^{-12}	Insignificant	0.56

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Comparably, hsa-miR-877-5p has been reported to function as an oncomiR in various forms of cancer. Previous studies have linked its upregulation to tumor progression, metabolic regulation, and poor survival outcomes in breast and lung cancers. A study examining microRNAs linked to bone metastasis in lung cancer identified hsa-miR-877-5p as a pivotal player in the miRNA-mRNA regulatory network related to apoptosis and metabolism.[30] Additionally, in research targeting common microRNAs associated with metabolic syndrome and breast cancer, hsa-miR-877-5p was noted as the only upregulated noncoding RNA in the plasma of PAM50 basal-like breast cancer patients. Target analysis showed decreased levels of IGF2 and TIMP3 transcripts in breast cancer tissues, correlating with poor patient survival rates. Furthermore, inhibiting hsa-miR-877-5p resulted in reduced growth and viability of triple-negative breast cancer cells, highlighting its potential as an oncomiR in this subtype of breast cancer.[31]

Target analysis in the present study indicated that reduced expression of the *FLI1* transcript was associated with poor prognosis in HNSCC. This observation suggests a potential regulatory relationship in which increased expression of hsa-miR-193b-5p may influence *FLI1* levels, thereby contributing to adverse clinical outcomes. *FLI1* encodes an ETS family transcription factor implicated in multiple cancer-related pathways, including cell proliferation and differentiation.[32] Although its role may vary across cancer types, our findings highlight a possible miRNA-gene interaction axis that warrants further investigation in the context of HNSCC.

MicroRNAs can function as oncomiRs or tumor suppressors depending on their specific targets and the cellular context within different cancer types. This dual role arises because a single miRNA can regulate multiple genes that may be oncogenes or tumor suppressors.[33] The tumor microenvironment, genetic and epigenetic alterations, and signaling pathways also influence miRNA targets and expression levels, thereby shaping their roles. Additionally, feedback loops and differential target abundance can shift the balance of miRNA effects.[34,35]

Mechanistically, chronic periodontal inflammation may promote carcinogenesis through sustained immune activation and release of inflammatory mediators, which in turn influence microRNA expression profiles. These dysregulated miRNAs can modulate key signaling pathways involved in cell proliferation, apoptosis, and immune evasion, thereby contributing to tumor development. The observed association between hsa-miR-193b-5p and its target gene *FLI1* further suggests a potential regulatory axis that may influence tumor behavior in HNSCC. From a clinical perspective, the identification of shared miRNA signatures between periodontitis and HNSCC highlights their potential utility as non-invasive biomarkers. Given that exosomal miRNAs are detectable in biological fluids, they may serve as candidates for liquid biopsy-based approaches in disease monitoring. However, these implications remain preliminary and require validation in clinical settings.

This study has several limitations. The discovery dataset was based on a small sample size (n=10), which may limit statistical power. Additionally, the findings are derived from in silico analyses and lack experimental validation. Functional enrichment analysis (e.g., GO/KEGG) was not performed in the present study, which limits the biological interpretation of the predicted targets. Furthermore, the exosomal localization was derived from publicly available databases and is not specific to HNSCC-derived vesicles, which should be considered when interpreting these findings. Therefore, further validation in larger cohorts and experimental studies is required. Future studies should focus on experimental validation of the identified microRNAs and their target genes, as well as functional characterization of their role in inflammation-driven carcinogenesis. Integration with proteomic and metabolomic data may further enhance understanding of the PD-HNSCC molecular axis.

Conclusion

This study identifies hsa-miR-193b-5p and hsa-miR-877-5p as potential molecular links between periodontitis and head and neck squamous cell carcinoma. Their consistent upregulation and association with reduced overall survival suggest a possible role in inflammation-associated carcinogenesis. The involvement of target genes such as *FLI1* further supports a potential regulatory mechanism underlying disease progression. However, these findings are based on computational analysis and a limited sample size and therefore require experimental validation and confirmation in larger clinical cohorts before clinical application.

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Additional information

Ethical statement

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The study uses computational analysis of publicly available datasets and therefore requires no ethical statement.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Conflict of interest

The authors have declared that no competing interests exist.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI. No writing assistance was utilized in the production of this manuscript.

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Author contributions

AP: conducting analysis, writing original draft; JVP: conceptualization, result analysis, interpretation, consolidation of results, review of original draft.

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Data availability

All of the data that support the findings of this study are available in the main text.