

Research Article

Investigation on the Differentially Expressed Genes in HIGK Cells Treated with *T.denticola* and their Putative Association with HNSCC

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Abstract

Objectives: *Treponema denticola* (Td) is a bacterium commonly linked to periodontal diseases, but its role in head and neck squamous cell carcinoma (HNSCC) is not well understood. This study aimed to explore the role of differentially expressed genes (DEGs) in HNSCC HIGK cells treated with *T. denticola*.

Methods: An observational study design using computational tools was employed to identify associations between DEGs in HIGK cells infected with *T. denticola*. The GEOmibus dataset GSE207003 was used to pinpoint DEGs in Td-infected HIGK cells. Gene expression profiling and survival analysis for the top 25 genes were performed using the UALCAN database.

Results: Numerous DEGs were identified in HIGK cells infected with *T. denticola*. Among the top 25 genes, LAMC2 (p-value < 10⁻¹²), FN1 (p-value = 1.62 × 10⁻¹²), and TGFBI (p-value = 1.11 × 10⁻¹⁶) showed significant overexpression. These genes significantly impacted HNSCC patient survival, with high expression correlating with poor prognosis.

Conclusion: This study identified three key genes—LAMC2, FN1, and TGFBI—potentially linked to HNSCC development. While LAMC2 and FN1 are known oncogenes, TGFBI, typically a tumor suppressor, was found to act as an oncogene in this context. Experimental validation is needed to confirm the role of *T. denticola* in carcinogenesis

Keywords: Microbiome, *Treponema denticola*, survival, prognosis, HNSCC.

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Head and neck squamous cell carcinoma (HNSCC) is a pervasive and deadly cancer that predominantly comprises of squamous cell carcinomas. HNSCC poses a significant global health concern with an annual incidence of over 550,000 cases and is responsible for approximately 300,000 deaths.^[1] Oral squamous cell carcinoma (OSCC),

a prominent form of HNSCC, accounts for 30% of all cancers in India. Early diagnosis of HNSCC leads to a 70–90% chance of survival, underscoring the critical importance of early detection. However, the lack of effective early screening and diagnostic procedures remains a major obstacle in addressing HNSCC, contributing to high mortality rates,

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particularly in advanced stages.^[2] The oral microbiome harbors diverse exotic microorganisms that adapt to different physiological and pathological conditions.^[3] Microbial dysbiosis in the oral cavity gives rise to mild forms of illness, emerging as cavities to serious forms, contributing to changes in normal cells. There is insufficient evidence to definitively support an association between bacterial pathogens and cancer development. However, researchers have investigated how bacteria contribute to tumor formation.

In line with these facts, the present study was designed to investigate the association between differentially expressed genes during Td infection and HNSCC. *Treponema denticola* (Td) is a bacterium commonly associated with periodontal diseases. However, its role in HNSCC is poorly understood. Some studies have suggested a potential link between chronic periodontal infection and an increased risk of developing certain types of cancers, including HNSCC. Peng and team demonstrated that Td could directly promote OSCC cell proliferation with activation of the intracellular TGF- β pathway. A series of in vitro and in vivo experiments have been performed to confirm this association.^[4] Clinical researchers have found that patients with periodontal disease are at a higher risk of cancer and mortality. The presence of elevated regulatory T cells (Tregs) in these patients indicates a potential link to inflammatory responses from the oral microbiota. Chronic inflammation and immune responses triggered by periodontal pathogens such as Td may contribute to the development of cancer in the oral cavity.^[5]

Numerous studies have demonstrated the prevalence of Td in health and disease conditions. Td is present in low abundance in healthy individuals, while it is most prevalent in periodontal disease and linked to esophageal squamous cell carcinoma (ESCC), oral squamous cell carcinoma (OSCC), and colorectal cancer (CRC). Its protease dentilisin, associated with increased tumor invasion and recurrence, degrades IL-8 and TNF α and activates pro-MMP8 and pro-MMP9, promoting a proteolytic environment conducive to epithelial cell invasion. High dentilisin expression correlates with larger tumors and recurrence in patients aged < 60.^[6] Accumulating evidence has instigated research in this field of oral oncobiomes that could provide vital clues about the mechanisms connecting the two disease phenotypes. For several decades, computational approaches have been used to uncover the roles of gene families,^[7] gene networks,^[8] and epigenetic components^[9] in cancer development. This study aimed to explore the potential link between Td and the development of head and neck tumors using data from computational approaches.

Methods

Sample Dataset

The GEOmnibus dataset, GSE207003, was used in this study. The dataset comprised six samples of untreated HPV 16 immortalized gingival keratinocytes (HIGK) (GSM6267807, 808, 809, 810, 811, 812) and six samples of HIGK cells infected with *Treponema denticola* ATCC 35405 (GSM6267813, 814, 815, 816, 817, 818).^[10] The HIGK cells infected with Td were taken as the test group (<https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE207003>) and uninfected HIGK served as the control group. The p-value cutoff was set at 0.05 and the log 2-fold change threshold was set at 0. Benjamini and Hochberg's method was used to derive the adjusted p-values. As the analysis returned an exhaustive collection of differentially expressed genes (DEGs), only the top 25 genes were chosen for further analysis (Table 1, Fig. 1).

Gene Expression and Survival Analysis

The UALCAN database (<http://ualcan.path.uab.edu/cgi-bin/TCGA-survival>) was used to investigate the expression levels of the top 25 DEGs identified in the previous analyses. The primary tumor group comprised 520 patients with HNSCC and 44 normal samples. Expression profiles were measured in transcripts per million (TPM), a standard unit for normalizing RNA-seq data. Box-whisker plots were created using the TPM values to compare the significance between the different groups. Additionally, Kaplan-Meier analysis was used to demonstrate the overall survival of patients with HNSCC. This analysis compared the high-and low/medium-expression groups to show the relationship between gene expression changes and patients overall survival (OS).^[11]

Statistical Analysis

Gene expression data from multiple datasets were analyzed using GEO2R. GEO2R uses the R packages from Limma to normalize the RNA-Seq data, followed by the Voom function, which converts the RNA-Seq count data to log2 counts per million. The results are presented as tables and graphic plots. The UALCAN portal analyzes gene expression profiles by comparing expression levels between groups using a PERL script accompanied by the Comprehensive Perl Archive Network (CPAN) module. Survival plots were generated using the "survival" and "survminer" R packages and were further compared using the log-rank test. The "Kaplan Meier-survival" package was exclusively used for survival analysis, including survival curves, hypothesis tests, and models. Meanwhile, the "Survminer" package improved the visualization of Kaplan-Meier and forest plots, allowing for clearer representation and interpretation of complex survival data.^[12]

Table 1. The list of top 25 genes that were found to be differentially expressed in HIGK infected with *Treponema denticola* Vs uninfected HIGK

Symbol	Description	Gene expression	Log2 Fold Change	Adjusted p value
KIF2C	Kinesin family member 2C	Downregulated	-1.72	0.00
LAMC2	Laminin subunit gamma 2	Upregulated	1.59	0.00
HK2	Hexokinase 2	Upregulated	0.98	0.00
IL36G	Interleukin 36 gamma	Upregulated	7.01	0.00
FN1	Fibronectin 1	Upregulated	2.71	0.00
CCL20	C-C motif chemokine ligand 20	Upregulated	4.47	0.00
CLDN1	Claudin 1	Upregulated	2.52	0.00
CXCL8	C-X-C motif chemokine ligand 8	Upregulated	4.03	0.00
CXCL1	C-X-C motif chemokine ligand 1	Upregulated	3.46	0.00
FHDC1	FH2 domain containing 1	Upregulated	1.79	0.00
TLR2	Toll like receptor 2	Upregulated	2.00	0.00
HMGB2	High mobility group box 2	Downregulated	-2.40	0.00
TGFB1	Transforming growth factor beta induced	Upregulated	1.31	0.00
GM2A	Ganglioside GM2 activator	Upregulated	1.46	0.00
SERPINB1	Serpin family B member 1	Upregulated	2.86	0.00
CFB	Complement factor B	Upregulated	4.14	0.00
TNFAIP3	TNF alpha induced protein 3	Upregulated	2.67	0.00
INHBA	Inhibin subunit beta A	Upregulated	3.22	0.00
IGFBP3	Insulin like growth factor binding protein 3	Upregulated	1.58	0.00
STEAP4	STEAP4 metalloredutase	Upregulated	3.83	0.00
CPA4	Carboxypeptidase A4	Upregulated	1.93	0.00
CTSB	Cathepsin B	Upregulated	2.94	0.00
MTSS1	MTSS I-BAR domain containing 1	Upregulated	1.82	0.00
NDRG1	N-myc downstream regulated 1	Upregulated	2.03	0.00
LCN2	Lipocalin 2	Upregulated	4.06	0.00

Results

GEO2R Analysis

The analysis of GSE207003 using GEO2R revealed the expression profile of more than 250 genes in HIGK cells infected with Td (Fig. 1). This result included up- and down-regulated genes that were differentially expressed in the HIGK-Td group. A set of the top 25 genes was selected based on their adjusted p-values from the collection and subjected to further analysis (Table 1). Among the top 25 genes, 2 genes were downregulated, viz., KIF2C and HMGB2, with a fold change value of -1.72 and -2.40, respectively. All other genes were upregulated with a minimum fold-change value of 0.98 (HK2) and a maximum value of 7.01 (IL36G). Repetitive genes, pseudo-genes, and non-coding RNAs were excluded from the study.

Gene Expression Analysis

The curated hub of 25 genes was investigated using the UALCAN database against the head and neck squamous cell carcinoma dataset. Among the 25 genes, three returned insignificant values, two exhibited downregulation, and 20 demonstrated upregulation. Approximately 18 genes

showed expression profiles similar to those observed in the HIGK-Td-infected dataset. The highest level of upregulation was observed with TGFB1, with a p-value of 1.11×10^{-16} and the lowest level of significance was observed for the TLR2 gene, with a p-value of 2.85×10^{-02} . Two genes, SERPINB1 (p-value = 3.79×10^{-06}) and LCN2 (p-value = 6.176×10^{-04}) were downregulated in the HNSCC dataset (Table 2).

Survival analysis

A correlation analysis was conducted between the gene expression profile and survival status of HNSCC patients. The Kaplan Meier plotter revealed three genes, LAMC2 (p-value = $<10^{-12}$) (Fig. 2), FN1 (p-value = 1.62×10^{-12}) (Fig. 3), and TGFB1 (p-value = 1.11×10^{-16}) (Fig. 4), which were strongly correlated with the survival of HNSCC patients. Interestingly, the expression profiles of the three genes were similar in both the datasets. All three genes were upregulated in the primary tumor group compared with the normal group. A significant change in the gene expression profile between patients with high and low/medium expression was exhibited by all three genes: LAMC2 (p=0.042), FN1 (p=0.051), and TGFB1 (p=0.023). Increased expression invariably leads to a poor prognosis.

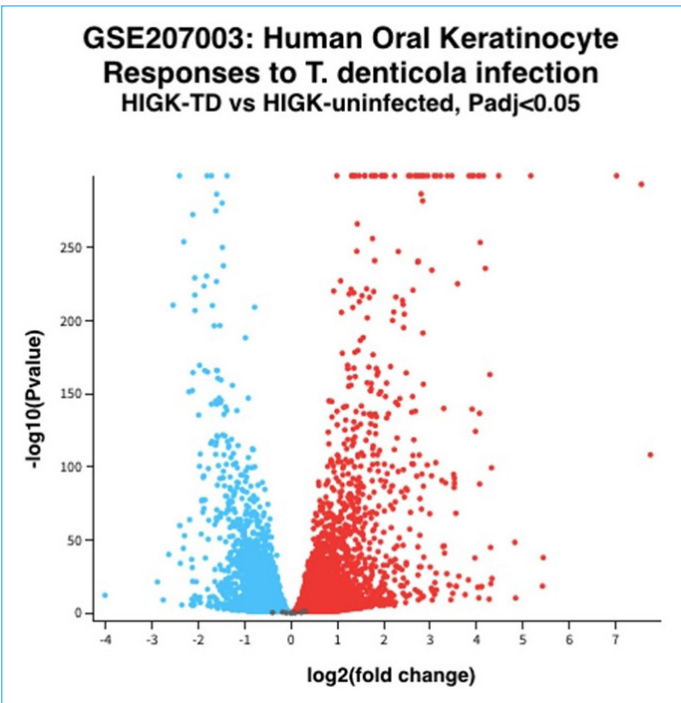


Figure 1. Volcano plot demonstrating differentially expressed genes in *Treponema denticola*-treated HIGK compared to uninfected HIGK. The blue dots represent downregulated genes, and the red dots represent upregulated genes. An adjusted p-value of less than 0.05 was considered significant.

Discussion

A delicate balance and intricate interplay between the host cells of the oral cavity and microbial cells maintains health. Cardiovascular diseases, autoimmune and metabolic disorders, and cancer emerge when the equilibrium is disrupted. The presence of specific oral bacteria, viruses, and yeast has been strongly linked to cancers of the head and neck region, esophagus, stomach, pancreas, colon/rectum, and lungs. These microbial associations may offer valuable insights into the early diagnosis and treatment of neoplastic diseases. Understanding the potentially significant role of the oral microbiota in cancer development will aid in devising more effective treatment strategies.^[13] Microarrays and gene expression profiling using RNA-Seq data analyzed using various computational and statistical tools have aided researchers in monitoring host cell responses to bacteria globally. These studies have provided valuable insights into host-microbe dynamics, potentially paving the way for innovative therapeutic, prophylactic, and diagnostic approaches.^[14]

Periodontal bacteria are crucial in connecting periodontal disease and oral cancer by creating a persistently imbalanced pro-inflammatory environment. Common periodontal pathogens, such as *Porphyromonas gingivalis*,

Table 2. The gene expression profile of top 25 DEG genes in head and neck squamous cell carcinoma dataset (TCGA, Firehose Legacy)					
Symbol	Gene expression In HIGK-infected with <i>T.denticola</i>	Gene expression profile in HNSCC dataset	p	Survival analysis	p
KIF2C	Downregulated	Upregulated	1.62×10^{-12}	Insignificant	0.75
LAMC2	Upregulated	Upregulated	$< 10^{-12}$	Significant	0.042
HK2	Upregulated	Upregulated	4.96×10^{-07}	Insignificant	0.93
IL36G/IL1F9	Upregulated	Upregulated	1.78×10^{-03}	Insignificant	0.89
FN1	Upregulated	Upregulated	1.62×10^{-12}	Significant	0.051
CCL20	Upregulated	Upregulated	3.69×10^{-06}	Insignificant	0.99
CLDN1	Upregulated	Upregulated	1.63×10^{-12}	Insignificant	0.89
CXCL8	Upregulated	Upregulated	7.28×10^{-09}	Insignificant	0.057
CXCL1	Upregulated	Insignificant	1.61×10^{-01}	Significant	0.0033
FHDC1	Upregulated	Insignificant	5.53×10^{-01}	Insignificant	0.36
TLR2	Upregulated	Upregulated	2.85×10^{-02}	Insignificant	0.59
HMGB2	Downregulated	Upregulated	$< 10^{-12}$	Significant	0.018
TGFB1	Upregulated	Upregulated	1.11×10^{-16}	Significant	0.023
GM2A	Upregulated	Upregulated	2.16×10^{-08}	Insignificant	0.9
SERPINB1	Upregulated	Downregulated	3.79×10^{-06}	Insignificant	0.85
CFB	Upregulated	Insignificant	6.04×10^{-01}	Significant	0.37
TNFAIP3	Upregulated	Upregulated	1.09×10^{-13}	Insignificant	0.43
INHBA	Upregulated	Upregulated	$< 10^{-12}$	Insignificant	0.24
IGFBP3	Upregulated	Upregulated	1.38×10^{-11}	Significant	0.11
STEAP4	Upregulated	Upregulated	8.81×10^{-03}	Insignificant	0.74
CPA4	Upregulated	Upregulated	3.82×10^{-02}	Insignificant	0.34
CTSB	Upregulated	Upregulated	1.13×10^{-12}	Insignificant	0.18
MTSS1	Upregulated	Upregulated	2.02×10^{-11}	Insignificant	0.59
NDRG1	Upregulated	Upregulated	$< 10^{-12}$	Insignificant	0.94
LCN2	Upregulated	Downregulated	6.176×10^{-04}	Insignificant	0.67

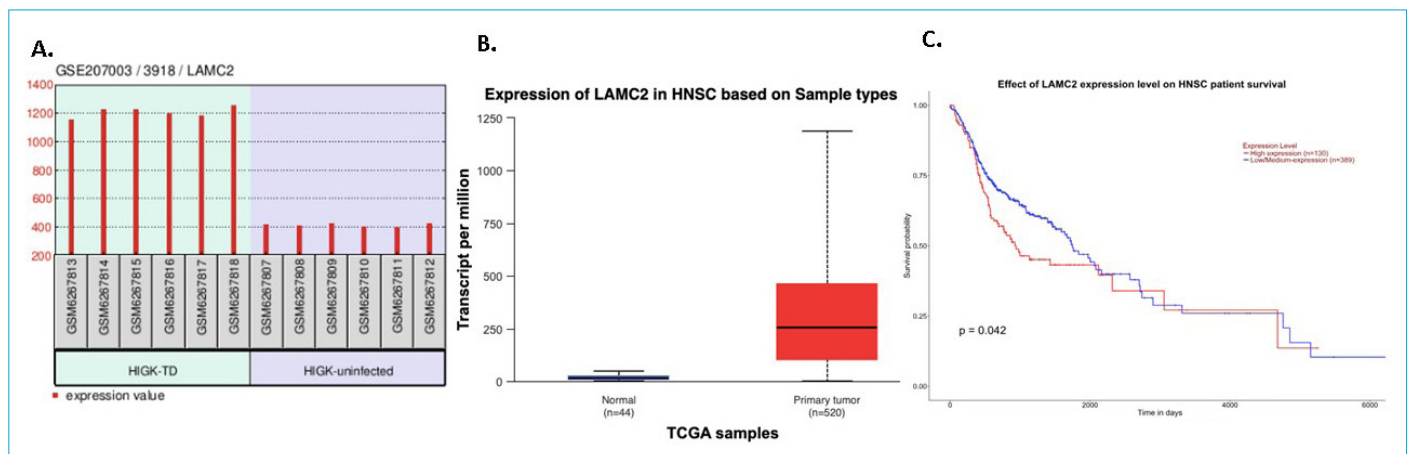


Figure 2. (a) Gene expression profile of LAMC2 gene in HIGK-infected with *T.denticola* Vs HIGK-uninfected, **(b)** Box Whisker plot demonstrating the gene expression profile of the LAMC2 gene in HNSCC datasets. The gene expression between the normal and the HNSCC primary tumor group demonstrated significant upregulation in transcript levels ($p\text{-value} = <10^{-12}$), **(c)** Kaplan Meier plot demonstrating survival probability of patients presenting with high and low levels of LAMC2 in HNSCC datasets. The patients exhibiting high expression of LAMC2 were found to have a poor prognosis ($p\text{-value} = 0.042$) when compared to the low-expression group.

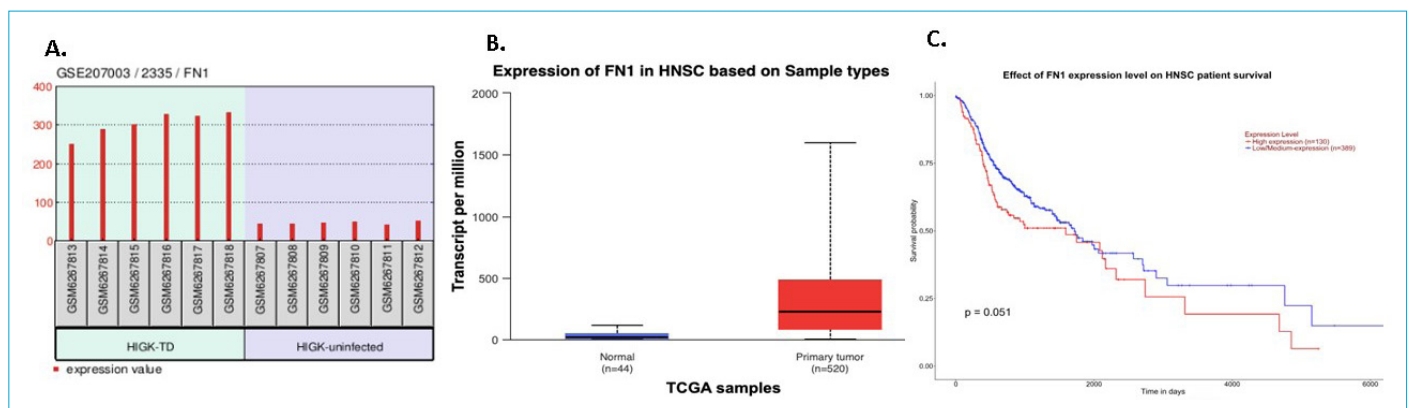


Figure 3. (a) Gene expression profile of FN1 gene in HIGK-infected with *T.denticola* Vs HIGK-uninfected, **(b)** Box Whisker plot demonstrating the gene expression profile of the FN1 gene in HNSCC datasets. The gene expression between the normal and the HNSCC primary tumor group demonstrated significant upregulation in transcript levels ($p\text{-value} = 1.62 \times 10^{-12}$), **(c)** Kaplan Meier plot demonstrating survival probability of patients presenting with high and low levels of FN1 in HNSCC datasets. The patients exhibiting high expression of FN1 were found to have a poor prognosis ($p\text{-value} = 0.051$) when compared to the low-expression group.

Fusobacterium nucleatum, and *Treponema denticola*, are frequently found in oral squamous cell carcinoma (OSCC) and have cancer-causing properties. These pathogens can attach to and invade oral epithelial cells, leading to cancer-associated characteristics such as inhibition of apoptosis, increased cell proliferation, and activation of epithelial-to-mesenchymal transition. Complex bacterial communities, including a combination of *P. gingivalis* and *F. nucleatum*, may strengthen the potential for cancer development. Transcriptomic data suggests that the functional properties of oral bacterial communities, rather than their composition, are more important in cancer development. A modified polymicrobial synergy and dysbiosis model has been proposed to explain the involvement of bacteria in OSCC.^[15] The molecular mechanisms underlying the asso-

ciation between periodontal infection and head and neck cancer are not well understood. Hence, the present study was carefully designed to identify differentially expressed genes in Td-infected HIGK cells and their putative association with HNSCC. This study identified three vital genes that showed similar gene expression profiles in the Td-infected and HNSCC datasets. The expression levels of LAMC2, FN1, and TGFBI were higher in primary tumor tissues than in normal tissues.

A systematic review and meta-analysis conducted by Fu et al. revealed that increased LAMC2 expression was markedly associated with lymph node metastasis, tumor-node metastasis stages, and tumor status, leading to poor survival rates in cancer patients.^[16] An experimental study by

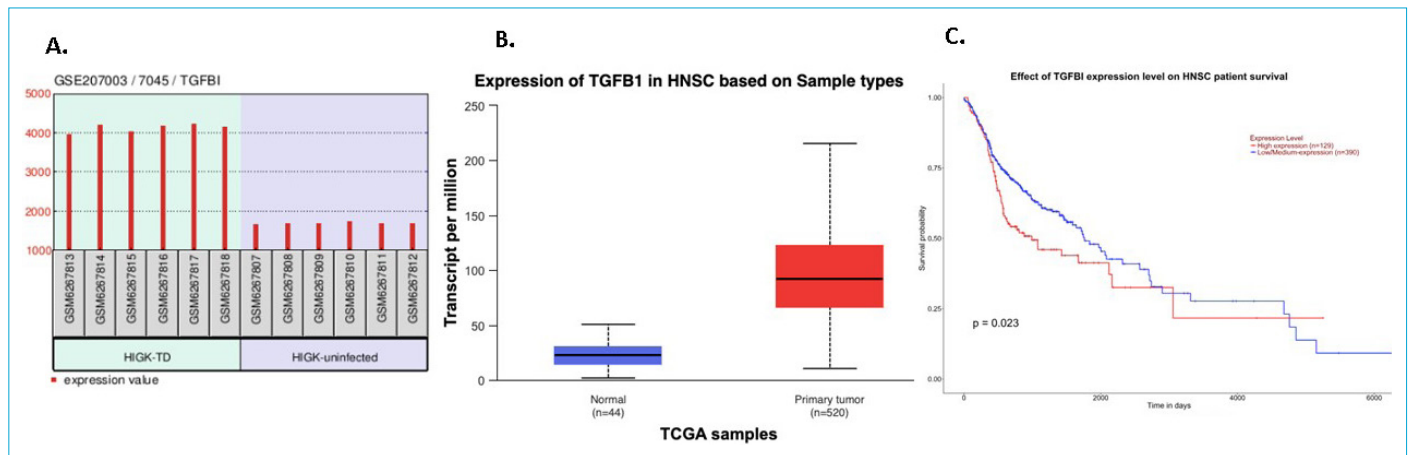


Figure 4. (a) Gene expression profile of TGFBI gene in HIGK-infected with *T.denticola* Vs HIGK-uninfected, (b) Box Whisker plot demonstrating the gene expression profile of the FN1 gene in HNSCC datasets. The gene expression between the normal and the HNSCC primary tumor group demonstrated significant upregulation in transcript levels ($p\text{-value} = 1.11 \times 10^{-16}$), (c) Kaplan Meier plot demonstrating survival probability of patients presenting with high and low levels of TGFBI in HNSCC datasets. The patients exhibiting high expression of TGFBI were found to have a poor prognosis ($p\text{-value} = 0.023$) when compared to the low-expression group.

Cave et al. investigated the role of LAMC2, a protein, in promoting metastatic traits in tumor-initiating cells. LAMC2-expressing cells showed enhanced self-renewal capacity, drove metastasis, and displayed a prominent squamous signature in mRNA profiling. Deregulation of the TGF- β signaling pathway was identified as a critical factor in promoting tumor growth and metastasis in LAMC2-expressing cells. This study adds to the observation that by targeting LAMC2, tumor aggressiveness in pancreatic cancer patients can be reduced.^[17] Previously, Wang et al. demonstrated that high expression of LAMC2 in laryngeal cancer was associated with lymph node metastasis and significantly influenced the overall survival of patients with LC. Treatment with cetuximab reduces the expression of LAMC2, thereby suppressing cell proliferation.^[18] The results of the present study agreed with those previously reported by other researchers. The laminin subunit gamma 2 encoding gene LAMC2 is part of the laminin family, which consists of α , β , and γ chains that assemble into a cross-shaped structure crucial for basement membrane integrity and cell-extracellular matrix (Extracellular matrix) interactions. Laminin γ 2, is specifically involved in the assembly and stabilization of the ECM, impacting cellular behavior and tissue architecture.^[19] A recent study by Shan et al. showed that LAMC2 interacts with autophagic machinery to regulate proliferation, invasion, and metastasis in oral squamous cell carcinoma (OSCC).^[20] A similar study by Tong et al. provided substantial evidence for the oncogenic properties of LAMC2 in lung cancer. They demonstrated that the overexpression of LAMC2 promoted EGFR membrane deposition and transport from the ER. An increase in the expression of LAMC2 prevents EGFR degradation.^[21] Interestingly, the

expression of LAMC2 was found to be elevated in chronic periodontitis (CP) patients when compared to those with gingivitis or normal healthy periodontium. It is noteworthy that increased expression of LAMC2 in the periodontitis group presenting with deep periodontal pockets probably reflects the intensity of the inflammation encountered during CP.^[22] Earlier, Song and team provided evidence on the increased expression of LAMC2 in deciduous periodontal ligament tissues, most probably related to the formation of extracellular matrix.^[23] Thus, the upregulation of LAMC2 during CP can contribute to tumor-promoting inflammation that inevitably leads to the remodeling of ECM during the development of potentially malignant conditions.

Fibronectin 1 (FN1) is a glycoprotein in the extracellular matrix associated with cancer progression. Wang et al. found that FN1 expression was linked to poor prognosis and increased macrophage infiltration, affecting the immune microenvironment in gastric cancer.^[24] A similar study investigated the clinical significance of FN1 in gastric cancer and its effects on the behavior of gastric cancer cells. The FN1 gene expression in gastric cancer tissues was assessed using immunohistochemistry staining, RT-PCR, and Western blotting. The study discovered that FN1 was increased in gastric cancer tissues and cell lines, and its expression was linked to tumor invasion, TNM stage, lymph node metastasis, and patient survival. When FN1 expression was inhibited, it significantly reduced cell growth, movement, invasion, and a process called epithelial-mesenchymal transition (EMT), and also increased cell death. These findings suggest that FN1 plays a role as an oncogene in gastric cancer, and its high expression may affect clinicopathological parameters and prognosis in gastric cancer patients.^[25] The present study

also presented a similar observation where the expression of FN1 was highly correlated with poor prognosis in HNSCC patients. FN is a well-established biomarker reflecting the periodontal status of individuals. A cross-sectional study investigated FN fragments in GCF from 94 subjects with untreated periodontitis. Western immunoblotting analysis revealed that the fragments (40-kDa, 120-kDa, 68-kDa) correlated with disease severity were identified, suggesting implications for disease diagnosis and management.^[26] The upregulation of FN observed in Td-infected cells and HNSCC patients strongly indicated the crucial role played by FN in the initiation of cancer. Much earlier reports have shown that Td has a unique tropism towards FN. The adhesion was known to promote chronic inflammation and induction of reactive oxygen species (ROS), which affects the nuclear material within the cells and modulates immune response so as to evade immune detection and clearance, leading to persistent inflammation and dysregulation of immune response.^[27]

The study has identified TGFB1, encoding transforming growth factor beta 1 (TGF-1), which plays a pivotal role in cancer. Initially, TGF-1 acts as a tumor suppressor, inhibiting cell proliferation and inducing apoptosis. However, in later stages of cancer, it promotes tumor progression through mechanisms such as epithelial-mesenchymal transition (EMT), angiogenesis, and immune suppression. TGF-1's involvement in these processes is mediated through SMAD-dependent and SMAD-independent signaling pathways. Elevated TGF-1 levels are often associated with poor prognosis clinically, making it a potential biomarker and therapeutic target in cancer treatment.^[28] The polarization of macrophages to an M2 state is triggered by TGFB1. These macrophages, often called tumor-associated macrophages, promote tumor growth, metastasis, and angiogenesis.^[29] A study by Wodzinski et al. evaluated TGFB1 gene expression in 64 patients with colorectal cancer (CRC), comparing it with clinicopathological features, promoter methylation, and TNM classification. The study suggested the gene's role in cancer progression.^[30] Interestingly, the expression of TGFB1 was shown to be increased in periodontitis patients.^[31] TGFB1 has a role in promoting wound healing and tissue repair processes during the resolution phase of inflammation. In cases of periodontitis, impaired TGFB1 signaling may impede proper tissue repair and regeneration, leading to chronic inflammation and disease progression. Elevated levels of TGFB1 may indicate a more severe form of periodontitis, potentially contributing to the transformation of normal cells into tumor cells.^[32] The present study showed the increased expression of TGFB1 in HNSCC patients, which corresponds to poor prognosis. Thus, investigating Td-induced genes using various experimental procedures

can provide a more comprehensive picture of their role.

The study has noteworthy limitations along with its merits. Firstly, using a computational approach in the study design needs validation through experimental approaches and in vivo models. Gene expression profiles can be influenced by carcinogen exposure, habits, infectious diseases, inflammatory conditions, age, gender, stage, and ethnic population. Therefore, a more controlled environment is necessary to provide concrete evidence about the association of microbial pathogens with cancer development. Although the study demonstrated the influence of candidate gene expression on patient survival, it's crucial to explore further the potentially more significant effects of microbe-induced epigenetic mechanisms on the prognosis of HNSCC patients.

Despite the advancements in the development of cancer therapeutics encompassing the CRISPR/Cas9 system,^[33] hybrid nanoparticles,^[34] and cancer diagnostics employing next-generation sequencing and engineered RGD peptides,^[35] there is a significant escalation in the number of cancer cases year after year. A more focused and diverse approach to investigating all the components with a special emphasis on the Oncobiome responsible for initiating cancer will provide more clues for developing theragnostic aids to combat cancer.

Conclusion

Recent advances in the field of oncomicrobiomes have opened up exciting opportunities for improving outcomes in cancer patients diagnosed at an early stage. By integrating the two fields of microbiome and oncobiology, researchers hope to gain a deeper understanding of the complex interactions between oral microbiome and host gene expression. They aimed to leverage this understanding to develop effective therapeutic strategies for diseases related to cardiovascular, cerebrovascular, metabolic, inflammatory, and autoimmune conditions. The present study is the first to provide insight into the genetic components related to Td-mediated development of HNSCC.

Disclosures

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Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – V.P.J., P.A.; Design – V.P.J., P.A.; Supervision – V.P.J., P.A.; Materials – A.P., B.K.; Data collection &/or processing – V.P.J., A.P., B.K.; Analysis and/or interpretation – V.P.J., A.P., B.K.; Literature search – A.R.A., V.P.J., A.P., B.K., P.A.; Writing – A.R.A., V.P.J., A.P., B.K.; Critical review – V.P.J., P.A.

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