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Functional transcriptomic profiling ofVeillonella parvula in oral microenvironments of patients with oral cancer: A cross-sectional study. Veillonella parvula Transcriptomics in Oral Cancer

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Abstract

Background.

Oral squamous cell carcinoma is a pathology associated with microbial dysbiosis. *Veillonella parvula* modulates the microenvironment by facilitating the maturation of complex biofilms; its role in carcinogenesis could therefore be decisive.

Objectives.

To determine the active biological processes of *Veillonella parvula* in saliva, dental plaque, and tumor tissue samples from patients with oral squamous cell carcinoma.

Methods

This cross-sectional study analyzed dental plaque, saliva, and tumor tissue from 10 oral squamous cell carcinoma patients. Following quality control (FastQC/Trimmomatic), Veillonella parvula was identified using Kraken and reference databases. Transcriptomic analysis (BLAST, STRING, KEGG) was performed on normalized data for differential abundance, clustering, PCA, and pathway enrichment. This approach characterized gene functions and identified tumor-associated signatures across microenvironments in a 69-word methodology.

CLINICAL TRIAL REGISTRATION

Not applicable. This study was observational and did not involve a clinical intervention.

1. INTRODUCTION

Oral cancer is a malignant neoplasm with high incidence and mortality worldwide. Oral squamous cell carcinoma (OSCC) is the most common subtype and is associated with a low survival rate [1]. Its etiology is multifactorial and involves chemical, physical, and biological factors; among the latter, oral dysbiosis associated with poor oral hygiene has been related to OSCC [2–5]. About 700 bacterial species have been identified in the oral cavity. Under healthy conditions, interactions between the host and microorganisms are maintained in a symbiotic balance, promoting the persistence of commensal microorganisms and an effective immune response [5]. Alterations in this balance may promote the formation of dysbiotic biofilms and the persistence of periodontal pathogens such as *Fusobacterium nucleatum, Porphyromonas gingivalis*, and *Prevotella intermedia*, leading to a reduction in commensal species and an increase in pathogenic microorganisms [2,3,6–8]. This dysbiosis may alter the bacterial gene expression patterns of beneficial bacteria while promoting the expression of genes associated with virulence and pathogenicity [7,9–11]. As a consequence, the production of carcinogenic bacterial

metabolites, such as acetaldehyde, nitrosamines, and reactive oxygen species (ROS), is increased, inducing epithelial damage and contributing to the process of carcinogenesis [12–14]. Recent studies have demonstrated a consistent association between periodontal pathogens and the tumor microenvironment [15]. Furthermore, inflammatory processes associated with periodontal disease generate environmental changes that increase the concentration of volatile sulfur compounds and metabolites, including lactic acid, acetic acid, butyric acid, and isocaproic acid. These metabolites can alter cellular behavior, induce DNA damage, and promote the proliferation and dissemination of tumor cells [9,11]. Similarly, the severity of periodontitis has been associated with increased DNA damage and enhanced carcinogenic effects of 4-Nitroquinoline-1-oxide, resulting in a greater number of cancerous lesions [9]. In this context, it is estimated that between 15% and 20% of tumors originate from infectious processes and chronic inflammation [16].

The study of the tumor microbiome through tools such as metagenomics, metatranscriptomics, and proteomics has enabled the characterization of both the composition and functional activity of microbial communities [17]. Several studies have identified bacterial profiles associated with periodontal disease in healthy individuals and patients with oral cancer. Reported species include *Achromobacter xylosoxidans, Aggregatibacter actinomycetemcomitans, Aggregatibacter aphrophilus, Campylobacter concisus, Haemophilus parainfluenzae, Lactobacillus gasseri, Leptotrichia buccalis, Olsenella uli, Porphyromonas gingivalis, Prevotella melaninogenica, Prevotella intermedia, Pseudomonas aeruginosa, Rothia dentocariosa, Rothia mucilaginosa, Streptococcus anginosus, Streptococcus constellatus, Streptococcus cristatus, Streptococcus gordonii, Streptococcus mitis, Streptococcus mutans, Streptococcus parasanguinis, Streptococcus salivarius, Streptococcus sanguinis, Tannerella forsythia, Treponema denticola*, and *Veillonella parvula* [18]. Furthermore, metatranscriptomic studies conducted in patients with OSCC have demonstrated the overexpression of virulence genes in periodontal pathogens related to iron transport, oxidative enzymes, and adhesin synthesis [12].

Veillonella species are commensal bacteria of the oral microbiome that play an important role in the ecological balance of oral biofilms and in metabolic interactions with other microorganisms. Their ability to metabolize lactic acid and participate in metabolic cross-feeding processes makes them key components of oral microbial dynamics. In the context of OSCC, several studies have reported changes in the abundance of *Veillonella* during disease progression, supporting a potential role for this genus in oral dysbiosis and carcinogenesis. [19,20]. An increased abundance of *Veillonella* has been observed in potentially malignant oral lesions and in the early stages of tumor development, whereas its abundance tends to decrease in advanced stages of OSCC [20]. *Veillonella parvula* stands out as a key species in dysbiotic biofilms [19]. *In vitro* studies indicate tha catalase production by *Veillonella parvula* may protect *Fusobacterium nucleatum* against oxidative stress [21]. In addition, this species may exert antitumoral effects through the production of propionate, a metabolite associated with the regulation of apoptosis and tumor metabolism [22]. These findings support a potential role for *Veillonella* may act as an ecological modulator of the tumor microenvironment by influencing inflammatory processes, biofilm organization, and metabolic signaling between the host and the microbiota [23, 24]. Therefore, *Veillonella*

species have emerged as potential microbiological biomarkers and promising therapeutic targets in oral cancer research.

Given that variations in the composition and function of the microbiome influence cancer susceptibility and progression, and considering that a significant proportion of tumors are associated with infections and chronic inflammation [25], it is essential to investigate the functional role of *Veillonella parvula* in OSCC to clarify its involvement in carcinogenesis and provide evidence regarding the underlying molecular mechanisms. In this context, the present study aims to investigate the functions and pathogenic mechanisms of *Veillonella parvula* in oral squamous cell carcinoma. The findings obtained may provide new perspectives for future research focused on the development of more effective therapeutic and preventive strategies for this disease.

2. MATERIALS AND METHODS

2.1. Study Design

A cross-sectional study was conducted to analyze the bacterial transcriptome in dental plaque, saliva, and tumor samples obtained from 10 patients with OSCC and 10 healthy individuals. The Ethics Committee of the Pontificia Universidad Javeriana approved the study protocol (Act No. 008B, June 5, 2014; code OD-0149).

2.2. Samples

Dental plaque, saliva, and tumor samples were collected from patients diagnosed with OSCC, while dental plaque and saliva samples were obtained from healthy controls with no history of malignant oral disease. Sample collection was performed under standardized biosafety and storage conditions to ensure the integrity of the biological material for subsequent transcriptomic analysis.

2.3. Data Processing

mRNA sequences obtained from the samples were stored in FASTQ format. Preprocessing was performed using Trimmomatic, applying a minimum quality threshold of Q20 and discarding reads shorter than 100 bp at the 3' end. Nextera adapters were removed, and reads containing low-quality nucleotides were filtered out. Data quality was assessed using FastQC by evaluating parameters such as quality score distribution, GC content, and adapter contamination. Human RNA and bacterial ribosomal RNA sequences were removed through a reference-based filtering approach. First, quality-filtered reads were aligned against the human reference genome/transcriptome using Bowtie to identify and discard host-derived sequences. The remaining non-human reads were subsequently screened against bacterial rRNA reference databases using tools such as SortMeRNA or similar short-read RNA filtering pipelines. Reads matching 16S, 23S, or 5S rRNA sequences were removed, and the final filtered dataset, enriched in bacterial mRNA, was retained for downstream taxonomic and functional transcriptomic analyses.

2.4. Taxonomic Identification

Veillonella parvula was taxonomically identified using Kraken Aligner v1.0 with the Kraken DB database, which includes complete bacterial genomes available in RefSeq (NCBI). The reference genome of *Veillonella parvula* (GenBank: LT906445.1) was obtained through the BV-BRC platform (Bacterial and Viral Bioinformatics Resource Center).

2.5. Bioinformatic Analysis

Transcriptomic data were analyzed using different bioinformatic tools. BLAST (Proksee) was used for the validation and visualization of genes expressed in dental plaque, saliva, and tumor samples. STRING DB was employed to identify protein–protein interactions and associated biological functions. Additionally, KEGG (Kyoto Encyclopedia of Genes and Genomes) was used for the characterization of metabolic pathways and molecular processes. The biological processes evaluated included metabolism, transport, genetic information processing, signaling/regulation, and structure/virulence. In addition, functional profiling of the metabolic genes detected in saliva, tumor tissue, and dental plaque was performed. Gene counts were normalized using the counts per million (CPM) method. To identify tumor-associated metabolic signatures, differential abundance analysis, hierarchical clustering, principal component analysis (PCA), and metabolic pathway enrichment analyses were performed. Additionally, the number of genes present in both groups was compared across five main functional categories. Standardized bioinformatic approaches were used for functional categorization and quantification.

3. RESULTS

3.1. Clinical characteristics of subjects

The mean age was similar between both groups (56.4 ± 18.36 years in patients vs. 56.5 ± 15.59 years in controls; p = 0.989). Regarding sex distribution, both groups showed an identical and homogeneous pattern, with a predominance of females (90%, n = 9) compared to males (10%, n = 1). Tumor location among patients with OSCC was heterogeneous, involving the tongue (50%), buccal mucosa (30%), and lip (20%) (Table 1).

Table 1
Clinical characteristics.

Characteristic	n (%) or mean ± SD
Age (years)	56.4 ± 18.36
Sex	
Female	9 (90.0)
Male	1 (10.0)
Tumor location	
Tongue	5 (50.0)
Buccal mucosa	3 (30.0)
Lip	2 (20.0)

A core set of 143 genes was identified across all studied microenvironments. A high distribution was found in dental plaque (395 genes) and tumor tissue (184 genes), whereas only 6 genes were detected in saliva. Comparative analyses revealed 83 genes shared between saliva and dental plaque, and only one gene shared between saliva and tumor (Supplementary material 1). With relation to abundance of *Veillonella párvula*, dental plaque exhibited the highest mean read abundance, followed by saliva and tumor tissue, which showed considerably lower values. Although this trend was observed, no statistically significant differences were detected between evaluated oral microenvironments ($p = 0.164$) (Supplementary material 2). Regarding the distribution of *Veillonella parvula* transcript reads, metabolic processes were the most abundant functional category, with approximately 260 reads. The second most abundant category was genetic information processing, with approximately 140 reads, followed by transport, with approximately 130 reads. Overall, metabolic processes represented the most abundant functional category, followed by genetic information processing and transport, whereas structure and virulence and regulation and signaling showed lower transcript abundance. In contrast, structure and virulence accounted for considerably fewer reads, with approximately 65, whereas regulation and signaling exhibited the lowest abundance, with approximately 50 reads. Although these categories were less abundant, they likely contribute to host interaction, environmental sensing, and bacterial adaptation within the oral ecosystem (Supplementary material 2).

3.2. Metabolic function of *Veillonella parvula*.

Dental plaque samples exhibited the highest abundance of metabolism-related genes. The greatest enrichment was observed in the "other pathways" category, with 213 genes, followed by amino acid/cofactor metabolism with 17 genes and glycolysis/ATP synthesis with 14 genes. Tumor samples showed an intermediate representation, whereas saliva exhibited the lowest abundance across most metabolic pathways (Fig. 1A). Most metabolic pathways were predominantly associated with dental plaque, particularly those involved in glycolysis/ATP synthesis, amino acid and cofactor metabolism, and

other core metabolic processes. Tumor samples exhibited selective enrichment of genes associated with anaerobic metabolism, stress response, DNA repair, and energy production, whereas saliva displayed a comparatively less active metabolic profile. Among the identified functional modules, glycolysis/ATP synthesis and amino acid/cofactor metabolism contained the largest number of highly expressed genes, whereas pathways involved in NAD metabolism, membrane transport, and DNA repair comprised fewer, but potentially niche-specific, transcripts. Overall, the network reveals a progressive shift in metabolic activity from saliva to dental plaque and tumor tissue, supporting the existence of microenvironment-dependent functional specialization of *Veillonella parvula* in patients with oral squamous cell carcinoma (Fig. 1B).

A. B.

3.3. Genetic information processing of *Veillonella parvula*.

Regarding the distribution of genetic information processing genes, dental plaque exhibited the highest abundance and diversity of expressed genes, particularly within the category of other genetic information processing functions (96 genes), followed by translation and ribosome-associated genes (26 genes), and DNA replication and repair genes (16 genes). In contrast, saliva and tumor samples exhibited fewer genes. Genes involved in translation and ribosome biogenesis were consistently detected across all microenvironments, with the highest abundance observed in dental plaque. Likewise, genes associated with DNA replication and repair were more abundant in tumor tissue and dental plaque than in saliva. Transcription-related genes were detected at low frequencies across all sample types, although their abundance was slightly higher in dental plaque (Fig. 2A). A clear predominance of genes involved in genetic information processing was observed in dental plaque. Most genes expressed in this microenvironment were associated with translation and ribosome biogenesis, DNA replication and repair, transcription, and other genetic information processing functions, indicating enhanced transcriptional and translational activity of *Veillonella parvula*. Genes involved in protein synthesis, including ribosomal proteins (*rpl* and *rps* families), elongation factors (*tuf* and *fusA*), and aminoacyl-tRNA synthetases (*tyrA, ileS, valS*, and *aspS*), formed a highly interconnected cluster, suggesting active cellular growth and protein production. The translation and ribosome biogenesis module exhibited the highest connectivity and gene representation in dental plaque, whereas the DNA replication and repair module comprised fewer genes but remained predominantly associated with dental plaque and tumor samples, indicating active cellular maintenance and genome stability mechanisms. Tumor samples displayed an intermediate level of connectivity, sharing several genetic information processing functions with dental plaque, whereas saliva exhibited the lowest number of associated genes, reflecting reduced genetic information processing activity (Fig. 2B).

A. B.

3.4. Transport function of *Veillonella parvula*.

Differences were observed in the distribution of transport-related genes across oral microenvironments. Dental plaque exhibited the highest abundance and diversity of transport-associated genes, particularly within the category of other transport processes, with 111 genes, followed by amino acid transport, with 13 genes, and metal ion transport, with 8 genes. In contrast, saliva and tumor tissue exhibited substantially fewer genes across most transport functions. Within the transport category, other transport processes represented the most abundant functional group across the three microenvironments, with the highest number of genes observed in dental plaque. Genes involved in amino acid transport were consistently detected in saliva, tumor tissue, and dental plaque, with the highest abundance observed in dental plaque. Similarly, genes associated with metal ion transport were more abundant in tumor tissue and dental plaque than in saliva indicating a potential role in adaptation to microenvironments with increased metabolic demand and oxidative stress. In contrast, genes involved in carbohydrate transport were detected at very low frequencies, suggesting that these pathways make only a limited contribution to the overall transport profile of *Veillonella parvula* (Fig. 3A). A strong predominance of transport-related genes was observed in dental plaque, with most genes clustered within the other transport processes module. This finding indicates that a substantial proportion of *Veillonella parvula* transport functions are concentrated in dental plaque and may contribute to enhanced nutrient acquisition and environmental adaptation. The amino acid transport module contained the largest number of representative genes and was predominantly associated with dental plaque, although it was also detected, to a lesser extent, in tumor tissue and saliva. Similarly, genes involved in metal ion transport showed moderate connectivity with tumor tissue and dental plaque. Carbohydrate transport contained only a limited number of representative genes and showed the lowest representation within the transport network. Conversely, other transport processes contained the largest number of representative genes, highlighting the broad representation of membrane transport systems, particularly in dental plaque. Tumor samples exhibited an intermediate level of connectivity, sharing several transport related functions with dental plaque but involving fewer associated genes. Saliva displayed the lowest connectivity and the smallest number of transport-related transcripts. (Fig. 3B).

A. B.

3.5. Structure and Virulence Function in *Veillonella parvula*.

The distribution of structure- and virulence-related genes differed across the oral microenvironments. Dental plaque exhibited the highest abundance and diversity of expressed genes, particularly within the "other structure/virulence" category, which comprised 58 genes, compared with 22 genes in tumor tissue and 14 genes in saliva. Genes associated with adhesion and surface structures were consistently detected across all microenvironments, with four genes identified in saliva, tumor tissue, and dental plaque. In contrast, the stress and survival factors category was detected almost exclusively in dental plaque, where two genes were identified, whereas minimal representation was observed in saliva and tumor tissue. Overall, dental plaque displayed the broadest representation of structure and virulence-related genes among the evaluated oral microenvironments. Adhesion- and surface-associated genes

showed higher expression in dental plaque than in the other microenvironments. Similarly, stress and survival factors were predominantly enriched in dental plaque (Fig. 4A).

Most genes classified within the other structure/virulence category were associated with dental plaque, forming the largest and most densely connected cluster in the network.

Dental plaque exhibited the broadest representation of structure- and virulence-related genes compared with saliva and tumor tissue. The adhesion and surface structures module constituted the second most prominent cluster and included genes such as *yadA*, which is associated with bacterial adhesion and interactions with host tissues. These genes were consistently detected across all microenvironments, although their representation differed among saliva, tumor tissue, and dental plaque. A smaller but distinct cluster corresponded to the stress and survival factors module, comprising genes associated with adaptation to environmental stress conditions. Although this module contained relatively few genes, it was predominantly associated with dental plaque. Tumor samples exhibited an intermediate level of connectivity, sharing several structure- and virulence-related genes with dental plaque, whereas saliva displayed the lowest connectivity and the fewest associated genes. Overall, dental plaque exhibited the highest number of connections and associated genes within the structure- and virulence-related network (Fig. 4B).

A. B.

3.6. Regulation and signaling in *Veillonella parvula*.

A clear predominance of regulation- and signaling-related genes was observed in dental plaque, which exhibited the highest abundance and expression levels across all functional categories. The other regulation/signaling genes category constituted the largest functional group, with 44 genes detected in dental plaque, compared with 18 genes in tumor tissue and 10 genes in saliva. A clear predominance of regulation- and signaling-related genes was observed in dental plaque, which exhibited the highest abundance and expression levels within this functional category. The other regulation/signaling genes category constituted the largest functional group, with 44 genes detected in dental plaque, compared with 18 genes in tumor tissue and 10 genes in saliva. Overall, regulation- and signaling-related genes showed their highest representation in dental plaque. Genes associated with stress response regulation were detected at low frequencies across all sample types but were more abundant in dental plaque. Similarly, genes involved in two-component signaling systems were predominantly detected in dental plaque and were minimally represented in saliva and tumor tissue. Transcriptional regulation genes were also detected at low frequencies but followed the same pattern, exhibiting greater abundance in dental plaque than in the other microenvironments. Although these functional categories contained relatively few genes, they were consistently detected across the evaluated microenvironments, with greater representation in dental plaque (Fig. 5A). A predominance of regulation- and signaling-related genes was observed in the dental plaque microenvironment, which exhibited the highest connectivity with the other regulation/signaling genes module, forming the largest and most densely connected cluster in the

network. This pattern indicates that *Veillonella parvula* exhibits enhanced regulatory activity in dental plaque compared with tumor tissue and saliva. The other regulation/signaling gene module contained most representative genes, including regulators involved in environmental adaptation, cellular communication, and transcriptional control. The other regulation/signaling gene module contained the largest number of representative genes and exhibited the highest connectivity, particularly in dental plaque. Smaller but distinct clusters corresponded to stress response regulation, transcriptional regulation, and two-component signaling systems. Genes within these modules were predominantly associated with dental plaque and, to a lesser extent, tumor tissue. Although less abundant, two-component signaling genes were detected predominantly in dental plaque, with lower representation in tumor tissue and saliva. Tumor samples exhibited an intermediate level of connectivity, sharing several regulatory pathways with dental plaque, whereas saliva displayed the lowest connectivity and the fewest associated genes. Overall, the regulatory network showed the lowest connectivity in saliva, intermediate connectivity in tumor tissue, and the highest connectivity in dental plaque (Fig. 5B).

1. **B.**

3.7. Differentially expressed genes by *Veillonella parvula* in oral microenvironments

A distinct transcriptional profile of *Veillonella parvula* was identified across the oral microenvironments, with genes clustering according to both biological function and expression pattern. Hierarchical clustering clearly separated dental plaque from saliva, whereas tumor samples exhibited an intermediate transcriptional profile, sharing several highly expressed genes with dental plaque. The metabolic genes of *Veillonella parvula* exhibited their highest overall expression levels in dental plaque. Notably, genes involved in central carbon metabolism and energy production, including *atpA, atpB, nadD, ackA, adhE*, and *cbiE*, formed one of the largest expression clusters. These genes are associated with ATP synthesis, NAD metabolism, acetate production, anaerobic fermentation, and cobalamin biosynthesis. Several of these genes also showed moderate expression in tumor tissue, although their expression levels were generally lower than those observed in dental plaque (Fig. 6). The genetic information processing genes of *V. parvula* formed the second major cluster. Ribosomal proteins (*rpl* and *rps* families), elongation factors (*fusA* and *tuf*), aminoacyl-tRNA synthetases (*ileS, valS, aspS*, and *tyrA*), and DNA replication and repair genes (*dnaA, dnaK, recA*, and *gyrB*) were highly expressed in dental plaque and moderately expressed in tumor tissue. This expression profile was characterized by the higher expression of genes involved in protein synthesis, translation, DNA replication, and genome maintenance in dental plaque (Fig. 6). The transport of *Veillonella parvula* also exhibited pronounced enrichment in dental plaque. ABC transporter genes, including *artM, fhuC*, and *gsiA*, together with genes involved in amino acid uptake and metal ion transport, formed highly expressed clusters. Tumor samples shared several transport-related genes but at lower expression levels, whereas saliva displayed only limited transcriptional activity (Fig. 6). The genes related to the structure and virulence of *Veillonella párvula* encoding adhesion and surface-associated proteins, particularly *yadA*, together with envelope-associated genes such as *oprF*

and *mrcA*, were predominantly expressed in dental plaque. In contrast, genes associated with stress adaptation and survival, including *ftsX* and related envelope maintenance proteins, exhibited lower but consistent expression in tumor tissue (Fig. 6). The genes related to the regulation and signaling of *Veillonella párvula* showed lower expression than the other functional groups but exhibited clear microenvironment-specific patterns. Global transcriptional regulators, stress response regulators, and components of two-component signaling systems, including *cggR, clpP, dps, narX, rpoA*, and *relA*, were preferentially expressed in dental plaque. These genes coordinate environmental sensing, transcriptional regulation, stress adaptation, and metabolic homeostasis (Fig. 6).

4. DISCUSSION

The oral microbiome has gained increasing attention because of its potential role in tumor initiation and progression. It comprises a complex, dynamic, and specialized microbial ecosystem that plays a fundamental role in maintaining oral homeostasis under symbiotic conditions. However, disruption of this ecological balance leads to dysbiosis, which has been associated with the development of both oral and systemic diseases [6]. Poor oral hygiene is a major driver of oral dysbiosis, promoting chronic local inflammation, altering host immune responses, and potentially contributing to the initiation and progression of OSCC [6,7]. These observations are consistent with our findings, as 90% of patients with OSCC exhibited poor or fair oral health status. Under dysbiotic conditions, the oral microbiota may increase the production of virulence factors and bioactive metabolites capable of promoting carcinogenic processes, including enhanced cell proliferation, inhibition of apoptosis, DNA damage, epithelial barrier disruption, epigenetic alterations, and tumor cell invasion [6,7,26]. In parallel, dysbiosis may suppress the expression of genes associated with commensal microorganisms while promoting transcriptional programs involved in bacterial virulence, stress adaptation, and survival [2,12].

These observations indicate that the contribution of the oral microbiome to OSCC extends beyond changes in microbial composition or the relative abundance of individual bacterial species. Consequently, identifying bacteria associated with OSCC is insufficient to fully elucidate their role in oral carcinogenesis. Metatranscriptomic analysis provides functional insights by identifying actively expressed genes and revealing the molecular mechanisms that regulate bacterial adaptation, metabolism, survival, and pathogenicity within the tumor microenvironment. This functional approach complements taxonomic profiling and provides a more comprehensive understanding of host-microbiome interactions, ultimately supporting the identification of novel diagnostic, prognostic, and therapeutic targets in OSCC [6].

Although metatranscriptomic studies of *Veillonella parvula* in OSCC remain scarce, some studies suggest that this species plays an important role in the tumor-associated oral microbiome. Members of the genus *Veillonella* have been consistently detected with high prevalence and relative abundance in saliva [27–29], dental plaque [27], oral potentially malignant disorders [30], and tumor tissue [28–30] from patients with OSCC. These observations indicate that *Veillonella* is a common component of the

oral microbiome associated with oral carcinogenesis; however, its precise functional role and biological significance remain poorly understood.

Current evidence supports a potential role for *Veillonella* as an ecological modulator of the tumor microenvironment through its influence on inflammatory responses, biofilm organization, and metabolic crosstalk between the host and the resident microbiota [31]. Consequently, *Veillonella* species have emerged not only as potential microbial biomarkers of OSCC but also as promising candidates for microbiome-based therapeutic strategies. Nevertheless, defining the specific transcriptional programs activated by *Veillonella parvula* within different oral microenvironments remains essential to understanding how this bacterium adapts to the tumor niche and contributes to oral carcinogenesis.

In this context, the present study investigated the transcriptomic profile of *Veillonella parvula* across distinct oral microenvironments in patients with OSCC. Our findings demonstrate that *Veillonella parvula* exhibits microenvironment-dependent transcriptional responses characterized by differential expression of genes involved in metabolism, genetic information processing, transport, cell structure, virulence, and stress adaptation. These functional differences indicate that *Veillonella parvula* undergoes extensive metabolic and physiological reprogramming in response to the specific conditions of each microenvironment, particularly within the tumor. This adaptive transcriptional plasticity supports the hypothesis that *Veillonella parvula* actively contributes to the functional ecology of the tumor-associated microbiome rather than acting merely as a passive member of the oral microbial community.

The transcriptomic approach enabled the identification of actively expressed *Veillonella parvula* genes across multiple biological processes in dental plaque, saliva, and tumor tissue from patients with OSCC, providing functional insights that extend beyond conventional taxonomic profiling. By characterizing the metabolic, structural, and regulatory pathways activated in each microenvironment, our findings provide new evidence that *Veillonella parvula* dynamically remodels its transcriptional program according to local environmental conditions. This functional specialization suggests that the contribution of *Veillonella parvula* to oral carcinogenesis is likely mediated not only by its presence within the tumor-associated microbiota, but also by its capacity to adapt metabolically, interact with neighboring microorganisms, and respond to host-derived environmental cues.

The marked enrichment of genes involved in ATP synthesis (*atpA* and *atpB*), NAD metabolism (*nadD*), acetate production (*ackA*), anaerobic fermentation (*adhE*), and cobalamin biosynthesis (*cbiE*) demonstrates that *Veillonella parvula* maintains a highly active anaerobic metabolic program, particularly within dental plaque and, to a lesser extent, tumor tissue. These pathways support efficient energy production and biosynthetic capacity, indicating that *Veillonella parvula* is well adapted to the oxygen-limited conditions of mature oral biofilms. The continued expression of these genes in tumor tissue is consistent with the capacity of *Veillonella parvula* to maintain anaerobic metabolic activity within the tumor microenvironment, potentially contributing to bacterial persistence.

Our findings are consistent with those reported by Chang et al., who demonstrated that *Veillonella parvula* produces propionate, a major short-chain fatty acid capable of suppressing oral squamous cell

carcinoma cell proliferation and invasion while promoting apoptosis through inhibition of the TROP2/PI3K/AKT signaling pathway [20]. Although our study did not quantify bacterial metabolites, the transcriptional activation of central metabolic pathways supports the hypothesis that metabolically active *Veillonella parvula* populations may generate bioactive metabolites capable of influencing the tumor microenvironment. Likewise, Kefayat et al. demonstrated that intravenously administered *Veillonella parvula* selectively colonized murine breast tumors, significantly reduced intratumoral lactate concentrations, and decreased both tumor growth and metastatic burden, providing further evidence that the anaerobic metabolism of *Veillonella parvula* can directly modulate the metabolic landscape of tumors [22]. Collectively, these findings suggest that the biological role of *Veillonella parvula* in oral carcinogenesis may extend beyond microbial persistence to include metabolically mediated interactions with host signaling pathways, highlighting its remarkable metabolic adaptability and its ability to thrive within mature oral biofilms as well as the tumor microenvironment [20–22].

We also identified a marked enrichment of genes involved in protein synthesis and genome maintenance, indicating that *Veillonella parvula* maintains active biosynthetic machinery within dental plaque. Ribosomal proteins (*rpl* and *rps* families), together with the elongation factors *fusA* and *tuf*, reflect intense translational activity and sustained protein production, whereas aminoacyl-tRNA synthetases (*ileS*, *valS*, *aspS*, and *tyrA*) ensure translational fidelity. In parallel, *dnaA*, *recA*, and *gyrB* participate in DNA replication, repair, and chromosome maintenance, while *dnaK* contributes to protein quality control and protection against cellular stress. Collectively, these genes indicate a metabolically active bacterial population capable of continuous growth, efficient protein synthesis, and maintenance of genome integrity within the plaque biofilm.

These findings agree with previous transcriptomic studies demonstrating that genes involved in translation, protein synthesis, and DNA maintenance represent highly active functional groups in *Veillonella* inhabiting oral biofilms [33]. The coordinated activation of these biosynthetic pathways suggests that *Veillonella parvula* not only maintains cellular homeostasis but also possesses the transcriptional flexibility required to sustain the production of bioactive metabolites that may influence host signaling pathways and facilitate adaptation to the oral and tumor microenvironments [20].

Additionally, transport-related genes were highly enriched in dental plaque, particularly the ABC transporter components *artM*, *fhuC*, and *gsiA*, together with genes involved in amino acid uptake and metal ion transport. The coordinated expression of these transport systems suggests an enhanced capacity for efficient nutrient acquisition and maintenance of metal homeostasis, both of which are essential for bacterial growth and survival within the highly competitive environment of mature oral biofilms. Their moderate expression in tumor tissue further indicates that similar nutrient acquisition strategies may support the persistence of *Veillonella parvula* within the metabolically heterogeneous tumor microenvironment.

In line with this, previous transcriptomic studies have shown that transport systems represent one of the most transcriptionally active functional groups in *Veillonella* during growth within oral biofilms and

carious lesions, highlighting their importance for ecological adaptation and persistence [33]. Similarly, Wei et al. demonstrated that the increased biomass and virulence of multispecies biofilms promoted by *Veillonella parvula* depend on efficient nutrient acquisition and enhanced stress tolerance [35]. Although their study did not specifically investigate the transport genes identified here, the elevated expression of *artM*, *fhuC*, and *gsiA* provides a plausible molecular basis for the enhanced nutrient uptake capacity required to sustain biofilm development, ecological fitness, and long-term persistence of *Veillonella parvula* within complex oral microbial communities.

Finally, genes involved in bacterial adhesion and cell envelope organization were predominantly expressed in dental plaque, particularly the adhesin gene *yadA*, together with the envelope-associated proteins *oprF* and *mrcA*. The coordinated expression of these genes is consistent with functions related to bacterial adhesion, cell envelope integrity, and biofilm maturation, which may contribute to the stable colonization of oral biofilms. In addition, the expression of *ftsX*, a gene involved in cell wall maintenance and stress adaptation, indicates that *Veillonella parvula* activates protective mechanisms that promote bacterial survival under adverse environmental conditions, including those encountered within tumor tissue. These results are consistent with previous studies describing *Veillonella parvula* as a key bridging species during oral biofilm development, facilitating physical and metabolic interactions with streptococci and other early colonizers that contribute to biofilm maturation and ecological stability [32]. More recently, Wei et al. demonstrated that *Veillonella parvula* also functions as a synergistic pathobiont capable of enhancing extracellular polysaccharide production, acid tolerance, and the virulence of *Streptococcus mutans* within multispecies biofilms [35]. Although neither study evaluated the transcription of the structural genes identified in our analysis, the predominance of *yadA*, *oprF*, *mrcA*, and *ftsX* provides a molecular basis that may explain the enhanced adhesive capacity, biofilm stability, and persistence of *Veillonella parvula* within complex oral microbial communities.

Although regulation- and signaling-related genes represented the smallest functional category, several key regulatory elements were preferentially expressed in dental plaque, indicating that *Veillonella parvula* actively coordinates adaptive responses to environmental fluctuations. The expression of the global regulator *cggR* is consistent with tight regulation of carbon metabolism, whereas components of two-component signaling systems, including *narX*, are involved in environmental sensing and metabolic adaptation. In addition, *relA*, *clpP*, and *dps* participate in the stringent response, protein homeostasis, and protection against oxidative stress, enabling the bacterium to maintain cellular integrity under adverse conditions. Collectively, the coordinated expression of these regulatory genes indicates that *Veillonella parvula* rapidly remodels its transcriptional program in response to changes in oxygen availability, nutrient supply, and host-derived stress.

These findings support the view of *Veillonella parvula* as a highly adaptable member of the oral microbiome, capable of responding dynamically to the physicochemical conditions of mature oral biofilms. The coordinated activation of carbon metabolism regulators, stress response proteins, and two-component signaling systems supports the ecological fitness of *Veillonella parvula* within complex

microbial communities and may also facilitate its persistence in the hypoxic and inflammatory tumor microenvironment [32].

Overall, the combined expression of metabolic, translational, transport, structural, and regulatory genes indicates that dental plaque provides the optimal ecological niche for *Veillonella parvula*, supporting active growth, biofilm establishment, and physiological adaptation. The partial conservation of this transcriptional activity in tumor tissue suggests that oral tumors share environmental characteristics with mature dental biofilms, thereby promoting bacterial persistence and potentially facilitating long-term host-microbe interactions during oral carcinogenesis. These results support the hypothesis that structural adaptation and host interaction mechanisms contribute to the persistence of *Veillonella parvula* in OSCC-associated ecosystems.

Together, the predominance of structure- and virulence-related genes in dental plaque reinforces the concept that *Veillonella parvula* actively contributes to the organization and functional stability of mature oral biofilms rather than acting as a passive commensal, an interpretation supported by Wei et al., who showed that *Veillonella parvula* functions as a synergistic pathobiont capable of enhancing *S. mutans* biofilm maturation, extracellular polysaccharide production, acid tolerance, oxidative stress resistance, and overall biofilm virulence [35]. Although Wei et al. did not investigate bacterial transcriptomes, the functional phenotype they described is supported by the transcriptional upregulation of adhesion-, envelope-, and stress-associated genes observed in our study, providing a molecular basis for the enhanced biofilm stability and persistence of *Veillonella parvula* within complex oral microbial communities.

Our findings are further supported by the metatranscriptomic study of Yost et al., which demonstrated that oral squamous cell carcinoma is associated not only with changes in microbial composition but also with extensive functional reprogramming of the oral microbiome [14]. The coordinated activation of genes involved in bacterial adhesion, nutrient acquisition, stress adaptation, and environmental sensing observed in our study is consistent with this concept, suggesting that *Veillonella parvula* undergoes microenvironment-specific transcriptional remodeling that enhances its ecological fitness and persistence within the tumor. Together, these studies support the view that the contribution of *Veillonella parvula* to oral carcinogenesis is determined not only by its presence within the microbial community, but also by its ability to dynamically regulate gene expression in response to local environmental conditions.

5. CONCLUSION

Transcriptomic analysis demonstrated that Veillonella parvula exhibits extensive functional specialization across oral microenvironments, characterized by active expression of genes involved in metabolism, nutrient transport, protein synthesis, virulence, and stress adaptation. The predominance of these transcriptional programs in dental plaque and their partial conservation in tumor tissue suggest that *V. parvula* is metabolically adapted to the tumor-associated oral ecosystem and may participate in host microbiome interactions relevant to oral carcinogenesis.

Declarations

COMPETING INTERESTS.

The authors declare that they have no financial or non-financial competing interests.

CONSENT FOR PUBLICATION.

Not applicable.

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Author Contribution

Conceptualization: Alveiro Erira, Adriana García. Data Curation: Alveiro Erira, Fabian Tobar, José Noguera. Formal Analysis: Alveiro Erira, José Noguera, Fabian Tobar, Litzi Colmenares. Investigation: Alveiro Erira, Adriana García, Fabian Tobar, Litzi Colmenares. Methodology: Alveiro Erira, Adriana García, Fabian Tobar. Supervision: Alveiro Erira, Adriana García. Validation: Alveiro Erira, Fabian Tobar, Adriana García, José Noguera. Writing–Original Draft: Alveiro Erira, Adriana García, Fabian Tobar, José Noguera, Litzi Colmenares. Writing–Review & Editing: All authors.

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Data Availability

Data Availability. The raw sequencing data analyzed in this study have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accession PRJNA1165312 (SRA Study SRP535088). The processed data generated from the bioinformatic analysis of Veillonella parvula are available in the Papyrus Research Data Repository under DOI 10.57924/G871NL.

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Figures

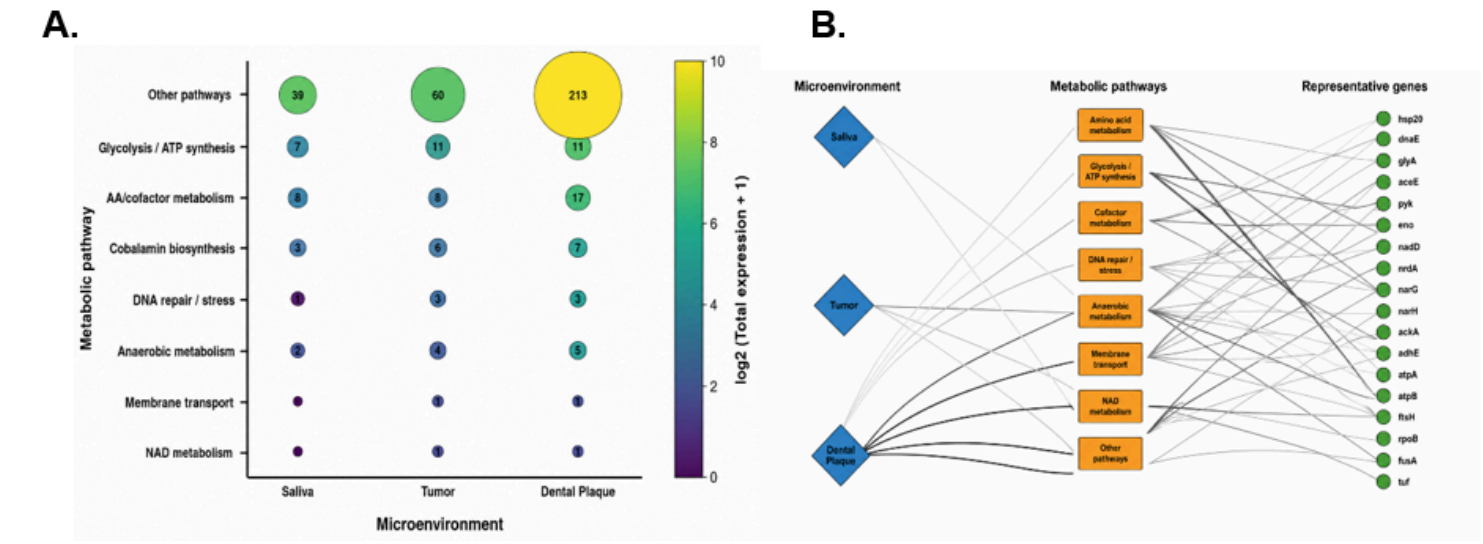


Figure 1

Distribution of metabolism-related genes by ***Veillonella parvula*** **across oral microenvironments (A)** Dental plaque exhibited the highest metabolic activity and gene representation across most pathways, followed by tumor tissue and saliva. **(B)** Relationships between oral microenvironments (saliva, tumor tissue, and dental plaque), metabolic pathways, and representative genes expressed by *Veillonella parvula* were identified.

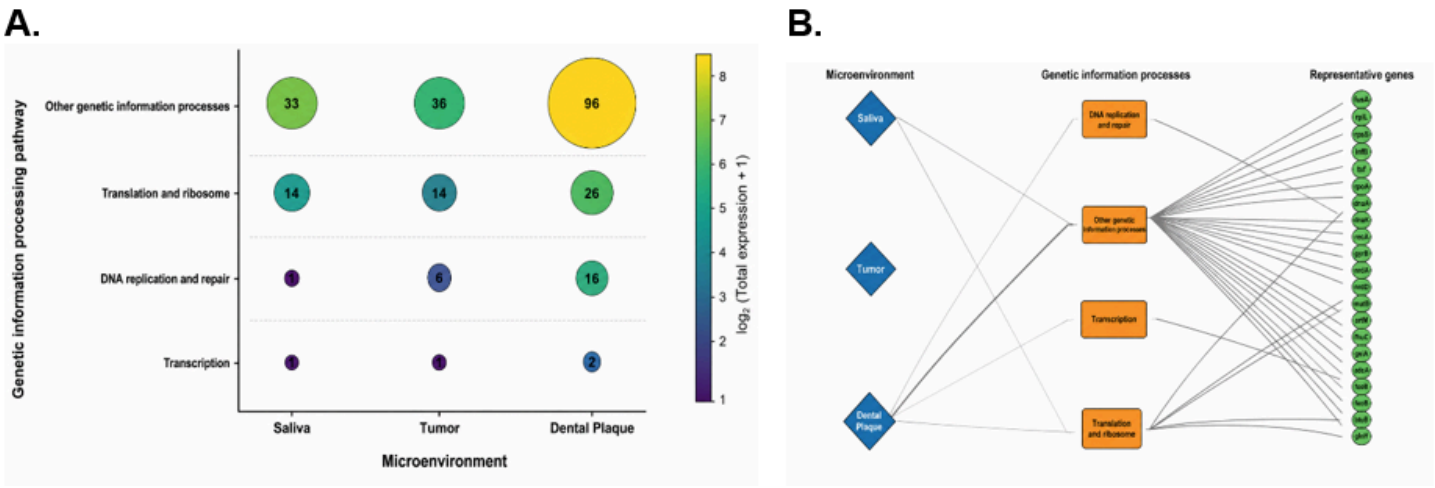


Figure 2

Genetic information processing of ***Veillonella parvula*** **in dental plaque, saliva, and tumor samples. (A)** Dental plaque exhibited the highest abundance and diversity of genes associated with genetic information processing compared with tumor tissue and saliva. **(B) Relationships** between oral microenvironments, genetic information processing functions, and representative *Veillonella parvula*genes. Dental plaque showed the highest association and gene representation, particularly in pathways related to translation, ribosome biogenesis, and DNA replication and repair.

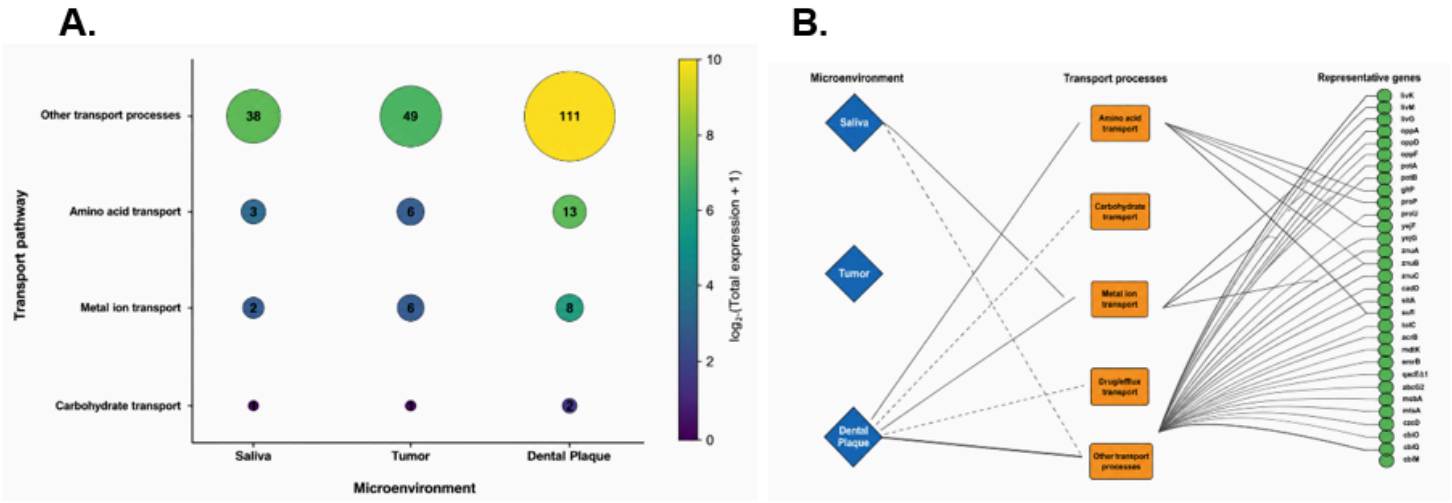


Figure 3

Transport-related genes of *Veillonella parvula*across oral microenvironments. **(A)**Distribution of transport-related genes in saliva, tumor tissue, and dental plaque according to transport pathway. Bubble size represents the number of genes, whereas color represents log2(total expression + 1). **(B)** Network representation showing the relationships among oral microenvironments, transport processes, and representative genes.

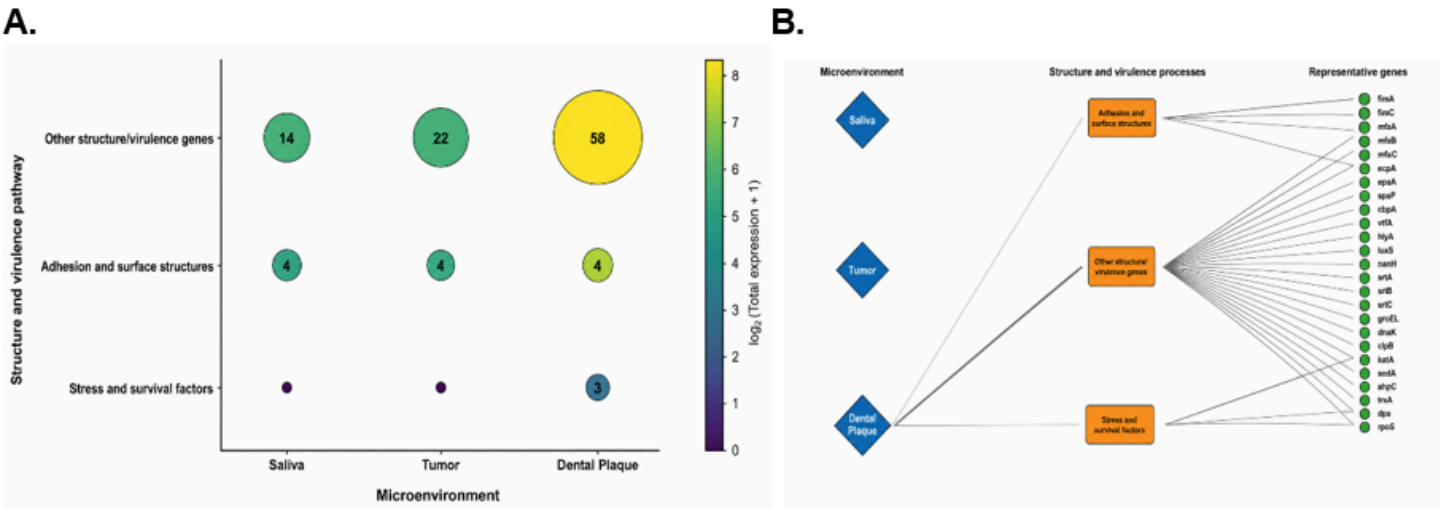


Figure 4

Structure- and virulence-related activity in *Veillonella parvula* in dental plaque, saliva, and tumor samples. A. Dental plaque exhibited the highest abundance and diversity of structure- and virulence-associated genes compared with tumor tissue and saliva. **B.** Relationships between oral microenvironments, structure- and virulence-related functions, and representative *Veillonella parvula* genes. Dental plaque exhibited the highest association and gene representation, particularly in adhesion, surface-associated, and stress response functions.

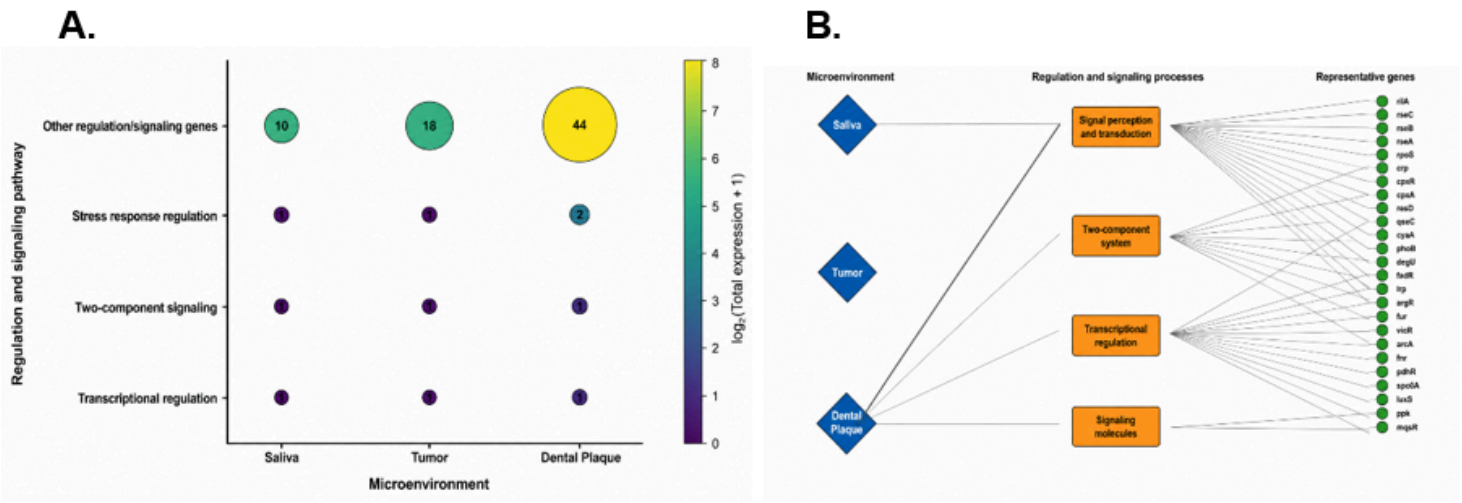


Figure 5

Regulation and signaling activity in *Veillonella parvula* in dental plaque, saliva, and tumor samples. A. Dental plaque exhibited the highest abundance and diversity of regulatory and signaling functions compared with tumor tissue and saliva. **B.** Relationships between oral microenvironments, regulation and signaling functions, and representative *Veillonella parvula* genes. Dental plaque exhibited the highest association and gene representation, particularly in regulatory, stress response, and environmental sensing pathways.

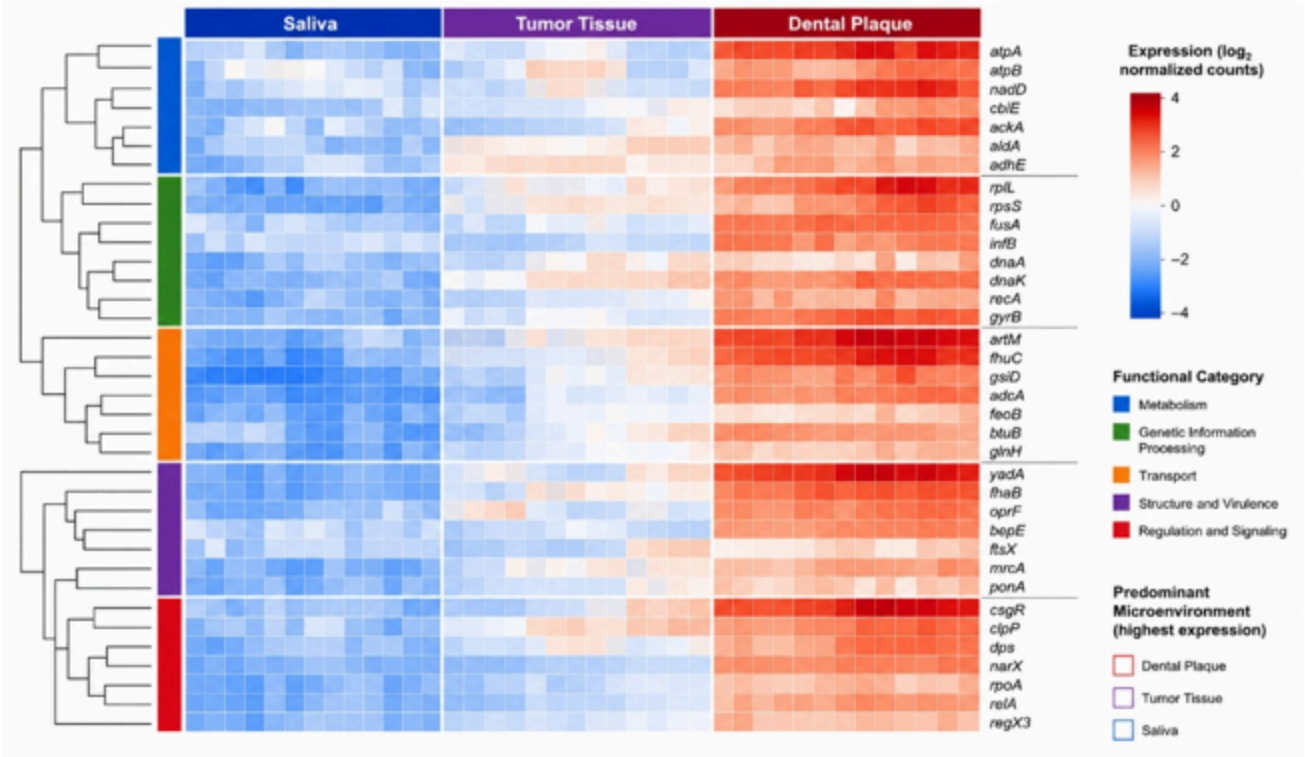


Figure 6

Expression patterns of differentially expressed *Veillonella parvula* genes across saliva, tumor tissue, and dental plaque. Genes are hierarchically clustered according to their expression profiles and functional categories, highlighting distinct transcriptional signatures among the three oral microenvironments.

Supplementary Files

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- ESM2.pdf
- ESM1.pdf