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Potential Common Molecular Mechanisms Between Periodontitis and Prostate Cancer: A Network Analysis of Differentially Expressed miRNAs

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Abstract

Background/Aim: Prostate cancer is the second leading cause of cancer-related deaths in men. Periodontitis is considered a high-risk factor for prostate cancer, but the genetic mechanism is unclear. This study aims to identify dysregulated miRNAs, their associated genes, signaling pathways, and compounds linking periodontitis to prostate cancer.

Materials and Methods: The miRNA expression datasets of prostate cancer and periodontitis were obtained from the GEO database. Differentially expressed miRNAs (DEmiRNAs) were identified, and common DEmiRNAs (Co-DEmiRNAs) between both datasets were determined. The Co-DEmiRNA-target network structure and functional analyses, including miRNet 2.0, were performed, encompassing Co-DEmiRNA-gene, Co-DEmiRNA-transcription factor (TF), and Co-DEmiRNA-compound networks. Functional enrichment analysis for Co-DEmiRNA genes and Co-DEmiRNA-TF networks was conducted using KEGG, Reactome pathways, and Gene Ontology (GO). Co-up and co-down DEmiRNAs were validated with TCGA miRNA-seq data.

Results: hsa-mir-148a-3p, hsa-mir-148b-5p, and hsa-mir-623 are the top miRNA nodes in Co-DEmiRNA-Target networks. The most significant candidate miRNA dysregulation genes are POU2F1, TMOD3, SCD, PRRC2C, and MAT2A, while the most important dysregulation TF includes TP53, CREB1, DNMT1, E2F1, and EGR1. Arsenic trioxide, gemcitabine, and 1,2,6-tri-O-galloyl-beta-D-glucopyranose are the most correlated compounds. Functional analyses revealed multiple cell signaling pathways, such as NOTCH and CREB phosphorylation, and regulation of processes, such as RNA metabolism and transcription.

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Conclusion: Our study suggests candidate molecular mechanisms linking periodontitis to prostate cancer, highlighting potential compounds targeting both diseases. These findings provide a foundation for guiding future basic and clinical research.

Keywords: Prostate cancer, periodontitis, network analysis, MicroRNA, genetic crosstalk.

Introduction

Prostate cancer (PC) is the second most common type of cancer in men worldwide, with approximately 375,000 deaths per year (1). Studies have identified various factors that increase the risk for PC, such as age, ethnicity, family history, lifestyle, diet, environmental exposures, prostatitis, and occupational factors (2). Periodontitis (PD) is a severe form of gum disease characterized by inflammation and infection of the tissues surrounding and supporting the teeth, caused by oral microbes, representing a significant cause of tooth loss in adults (3). Recently, researchers have focused on the association between periodontitis and the chance of developing cancer, particularly pancreatic, head and neck, and lung malignancies (4-6). Preliminary studies on the relationship between PC and PD have yielded conflicting results (7-9). However, two meta-analyses of seven and nine cohort studies in 2021 concluded that periodontal disease increases the frequency of PC by 1.17-fold (10) and 1.4-fold (11), respectively. Chronic inflammation, a hallmark of both conditions, may be a common underlying factor contributing to the PC and the PD relationship (3). Although a known correlation exists between PC and PD, the specific mechanisms that connect the two conditions are poorly understood and require further investigation.

Epigenetic and epitranscriptomic factors, critically regulate gene expression, play a crucial role in the development of PC (12-14). Among these factors, microRNAs (miRNAs), which are small RNAs, mediate the pathogenesis of many diseases by modulating various cellular processes. Identifying disease-related miRNAs and their dysregulation patterns may effectively elucidate the molecular pathogenesis of diseases (15). Additionally, such miRNAs may serve as potential biomarkers or therapeutic drug targets (16). Integrative bioinformatics has been used successfully to comprehend the secretion of miRNAs in oral diseases and identify these miRNAs as biomarkers for periodontal diseases (17). Interestingly, dysregulated miRNAs in periodontitis are not confined to tissues; they may influence gene expression at distant places, potentially via exosomal carriers. In this regard, the current work seeks to undertake an integrative investigation of miRNA release patterns in PD and PC. We analyzed the genetic data available on the GEO database to conduct an integrated study of both diseases. The purpose is to find potential miRNA linkages, linked genes, signaling pathways, and chemicals. The main goal is to improve knowledge of molecular linking mechanisms in these disorders and lay a theoretical platform for future fundamental and clinical research.

Materials and Methods

Microarray data. The periodontitis and prostate cancer datasets were downloaded from the GEO database (Table I) (https://www.ncbi.nlm.nih.gov/geo/). For analysis, the periodontitis miRNA expression dataset, GSE54710 (obtained from the Agilent-031181 Unrestricted_Human_miRNA_V16.0_Microarray 030840 platform), and the prostate cancer miRNA expression datasets, GSE21036 and GSE64318 (both obtained from the Agilent-019118 Human miRNA Microarray 2.0 G4470B), were identified.

Differential expression of miRNA (DEmiRNA) analysis. Microarray raw data for the specified samples were downloaded from the GEO database. GeneSpring Software version 14.9_gx_pa was used to obtain differentially

Table I. *Datasets used for analysis of periodontitis and prostate cancer.*

Disease	Accession	Platform	Case	Control	Total
Periodontitis	GSE54710	GPL15159	159	41	200
Prostate cancer	GSE21036	GPL8227	112	28	140
Prostate cancer	GSE64318	GPL8227	27	27	54
Prostate cancer	TCGA_PRAD	miRNA-Seq	494	52	546

expressed miRNAs (DEmiRNA) both comparing with the periodontitis and normal gum tissues and, comparing with the prostate cancer and normal prostate tissues. During the identification of DEmiRNAs, *t*-test was performed between periodontitis and normal gum tissues, and prostate cancer tissues and normal prostate tissues. The criteria were set as follows: *p*-Value <0.05, fold change >2.0, and false discovery rate was reduced using the Benjamini-Hochberg multiple testing correction.

Shared DEmiRNA analysis and Co-DEmiRNA definition. The DEmiRNA lists for both diseases were processed using the "VennDiagram" R package (http://cran.r-project.org/web/packages/VennDiagram/index.html) to obtain shared DEmiRNAs. These were considered as mutually expressed DEmiRNAs and subjected to further analysis. miRNAs exhibiting a common expression trend (both high and low expression) were defined as Co-DEmiRNAs, while shared DEmiRNAs with different expression trends (opposite expression) were excluded, as they did not contribute to disease-related studies.

Co-DEmiRNA-target network construction and functional enrichment analyses. Co-DEmiRNA target networks were constructed using miRNet 2.0 (https://www.mirnet.ca/). Target genes for the Co-DEmiRNA-gene network were selected from three databases (miRTarBase v8.0, TarBase v8.0, and miRecords). To reduce network complexity and preserve key features showing network connections, a "minimum network" was chosen. All starting or query nodes were utilized in the calculation. To create the "minimum network", shortest paths between pairs of starting nodes were determined, and nodes not on the shortest paths were removed. The same approach was used for a Co-DEmiRNA-transcription factor (TF) network created using TransmiR v2.0 and a Co-DEmiRNA-small molecule network based on SM2miR and PharmacomiR data. Functional enrichment analysis for KEGG, Reactome pathways, and Gene Ontology (GO) was performed using the hypergeometric test algorithm for both Co-DEmiRNA-gene and Co-DEmiRNA-TF networks. The top 5 significantly enriched functions were ranked with the "all genes" in the two minimum networks as the query set.

Validation of differentially expressed miRNA results in the TCGA cohort. The dbDEMC 3.0 database (https://www.picb.ac.cn/dbDEMC/) provides information on differentially expressed microRNAs in various cancer types from the recently published GEO and TCGA datasets (19). For validation of differentially expressed miRNAs in prostate cancer, we used the TCGA_PRAD prostate adenocarcinoma dataset (experiment ID EXP00403; 494 cases and 52 controls) from this database (Table I). *t*-test was performed, and the citeria were set as following: |logFC| >1 and *p*-Value <0.01.

Results

DEmiRNA and shared DEmiRNA identification. After filtering, 54 miRNAs associated with periodontitis were identified in the analysis of the GSE54710 dataset. For the analysis of the GSE21036 and GSE64318 datasets, 162 miRNAs associated with prostate cancer were identified (Supplementary Table I). When comparing periodontitis to controls, 39 DEmiRNAs were overexpressed, and 13

DEmiRNAs were underexpressed. Similarly, in prostate cancer, 73 miRNAs were overexpressed, while 87 miRNAs were underexpressed. The overlap between two lists of DEmiRNAs was investigated using a Venn diagram, revealing a total of 12 shared DEmiRNAs (Figure 1).

Corresponding expression patterns in the two conditions are depicted in Figure 2. When compared to control tissues in both conditions, similar expression patterns were evident in 8 shared DEmiRNAs; 6 shared DEmiRNAs showed overexpression, and 2 shared DEmiRNAs exhibited lower expression. Two shared DEmiRNAs, hsa-miR-219-5p and hsa-miR-375 demonstrated lower expression in tissues affected by periodontitis compared to controls, while showing overexpression in prostate cancer tissues. In addition, 2 shared DEmiRNAs, hsa-miR-145 and hsa-miR-486-5p, exhibited opposite expression patterns, with overexpression in periodontitis and low expression in prostate cancer. The distribution of shared DEmiRNAs between periodontitis and prostate cancer is shown in Table II.

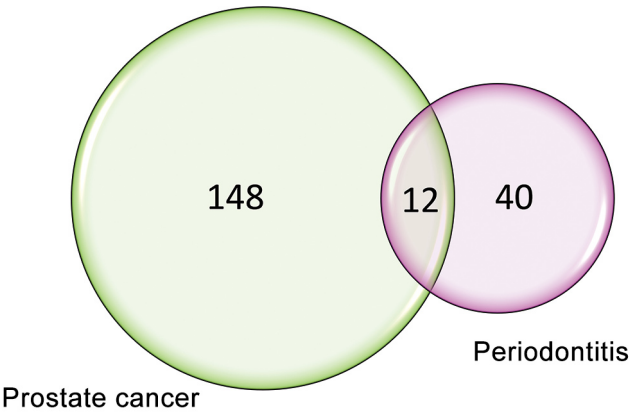

Figure 1. *Venn diagram showing shared differentially expressed miRNAs (DEmiRNAs). A total of 12 shared DEmiRNAs were revealed whose expression was altered between prostate cancer and periodontitis.*

Co-DEmiRNA identification, Co-DEmiRNA-gene network, and functional analysis. Co-DEmiRNA-gene network: The Co-DEmiRNA-Gene minimum network, comprising 48 genes and 16 miRNAs, is a network with 164 edges (Figure 3A, Supplementary Table II). The highest-degree DEmiRNA nodes in the network were hsa-mir-148b-3p, hsa-mir-148a-3p, and hsa-mir-623. Among the top 5 gene nodes with the highest degree in the network were *POU2F1*, *TMOD3*, *SCD*, *PRRC2C*, and *MAT2A*. The top 5 enriched functions for each are listed in Table III. Reactome analysis revealed highly enriched pathways, such as 'CREB phosphorylation through the activation of CaMKII', 'Ras activation upon Ca2+ infux through NMDA receptor', 'Transmission across Chemical Synapses', 'CREB phosphorylation through the activation of Ras', 'Trafficking of AMPA receptors'. GO biological process analysis showed regulation of many processes, such as cellular organization and developmental processes. Among the most enriched GO molecular functions were functions related to oxygen and protein binding, as well as receptor activities. Among the most enriched GO cellular components were endosome, cytosol, early endosome, and membrane-bounded vesicle.

Co-DEmiRNA-TF network: The Co-DEmiRNA-TF minimum network represents a network consisting of 16 TFs and 2 miRNAs, with a total of 18 edges (Figure 3B, Supplementary Table III). Among the top TFs are TP53, CREB1, DNMT1, E2F1, and EGR1, with two miRNA nodes, hsa-mir-148a and hsa-mir-202, in the network (Figure 3B). The enriched KEGG, Reactome, and GO pathways are listed in Table III. Among these are pathways related to signaling by NOTCH, factors involved in megakaryocyte development and platelet production, and various pathways related to CREB phosphorylation in Reactome. GO BP pathway analysis included pathways involving both negative and positive regulation of processes, such as RNA metabolism and transcription. Among the increasing GO molecular functions among TFs in the network, various functions related to transcription were found.

Co-DEmiRNA-small molecule network: The Co-DEmiRNA-Small Molecule minimum network represents a network consisting of 3 compounds and 4 miRNAs, with a total of 6 edges (Figure 3C, Supplementary Table IV). Among the 3 compounds in this network are arsenic trioxide,

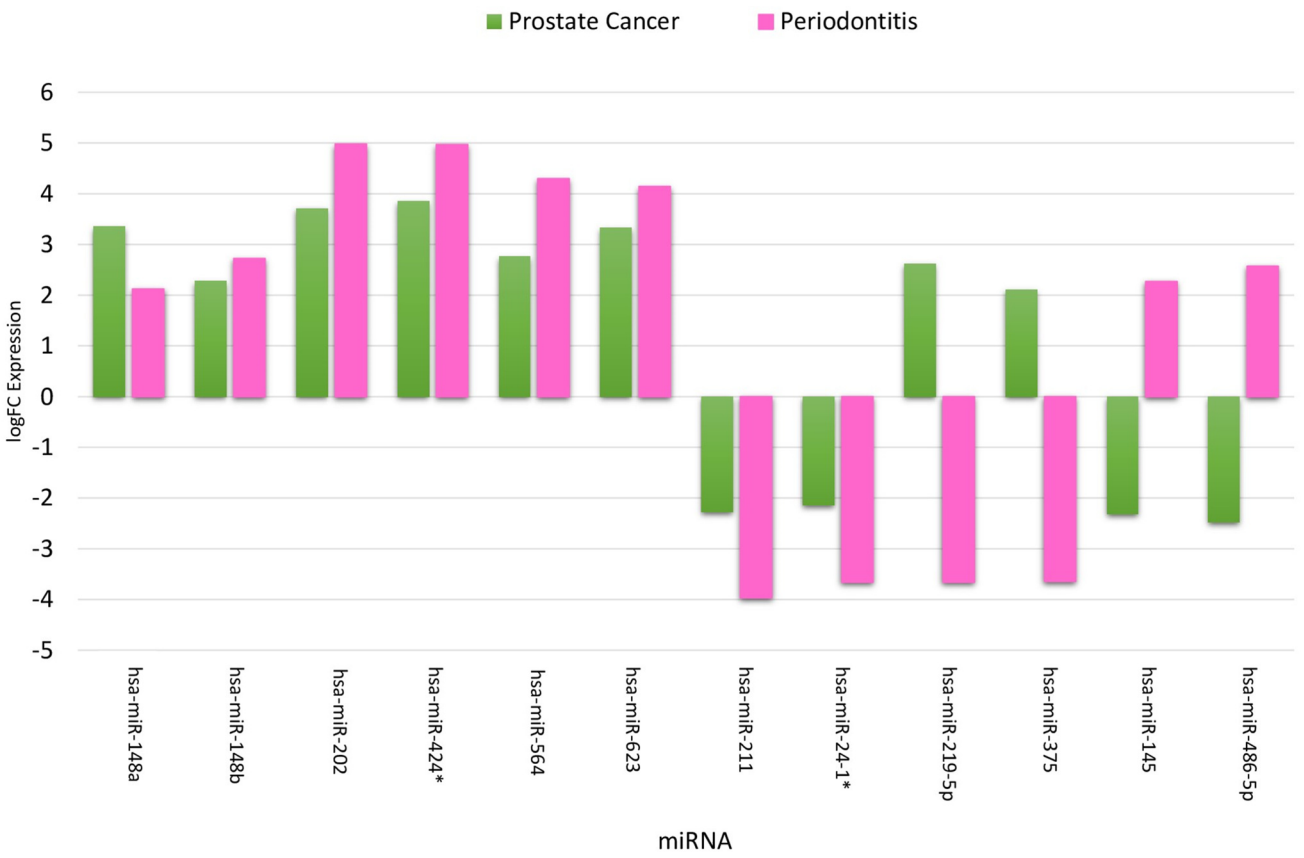

Figure 2. *Column charts showing log fold change (log FC) expression values of shared differentially expressed miRNAs (DEmiRNAs) in prostate cancer and periodontitis. In prostate cancer and periodontitis tissues, compared to control samples, 8 common differentially expressed miRNAs (DEmiRNAs) exhibited similar expression patterns. Among these, 6 DEmiRNAs were upregulated, while 2 were downregulated. In addition, 2 shared DEmiRNAs exhibited opposite expression patterns.*

Table II. *Shared differentially expressed miRNAs (DEmiRNAs) of periodontitis and prostate cancer.*

Expression	DEmiRNA
Co-up-regulated	hsa-miR-148a, hsa-miR-148b, hsa-miR-202, hsa-miR-424*, hsa-miR-564, hsa-miR-623
Co-down-regulated	hsa-miR-211, hsa-miR-24-1*
Opposite	hsa-miR-219-5p, hsa-miR-375, hsa-miR-145, hsa-miR-486-5p

The asterisks (*) refer to different products from the same pre-miRNA.

gemcitabine, and 1,2,6-tri-O-galloyl-beta-D-glucopyranose (1,2,6-TGGP). The highest-degree and betweenness component in this network is 1,2,6-TGGP.

Validation of differentially expressed miRNA results in the TCGA cohort. To validate our results, we examined miRNAs differentially co-regulated in prostate cancer and periodontitis in a larger, independent prostate cancer cohort. To do this, we analyzed miRNA levels in the TCGA_PRAD cohort, which included 494 prostate cancers and 52 controls. Three miRNAs (miR-148a-3p, miR-148b-5p, and miR-24-1) selected for validation from this cohort

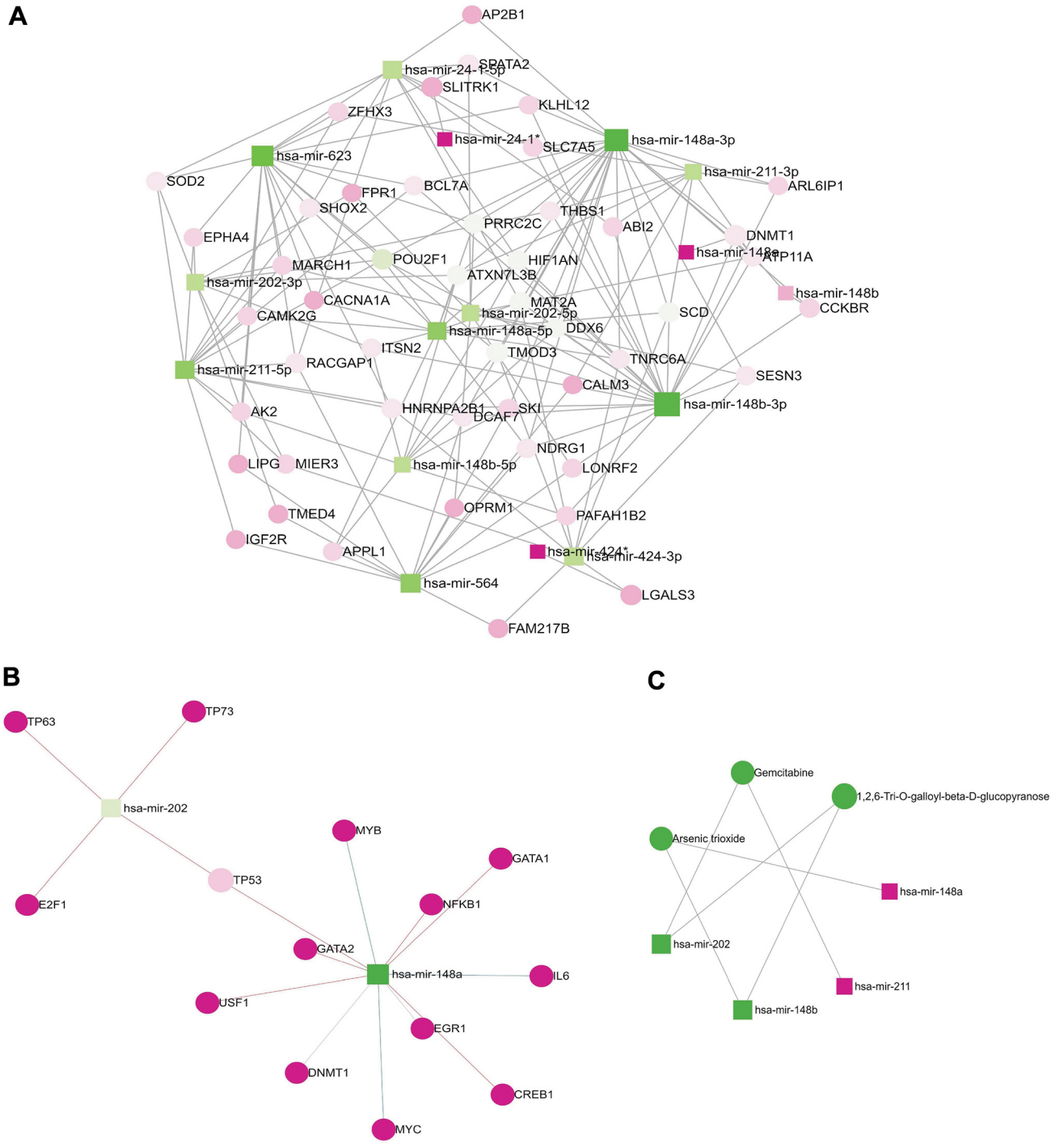

Figure 3. *Common differentially expressed miRNA (Co-DEmiRNA) networks. (A) Co-DEmiRNA-Gene network shows genes with common miRNA interactions between prostate cancer and periodontitis. (B) Co-DEmiRNA-Transcription Factor network shows transcription factors with common miRNA interactions between prostate cancer and periodontitis. (C) Co-DEmiRNA-Small Molecule network shows small molecules with common miRNA interactions between prostate cancer and periodontitis. The darker the color and larger the size of the key node in the figure, the higher its interaction degree.*

Table III. *Shared differentially expressed miRNA (DEmiRNA)-gene network pathways and DEmiRNA-transcription factor network pathways.*

DEmiRNA-gene network pathway		DEmiRNA-TF network pathway	
KEGG pathway	*p*-Value	KEGG pathway	*p*-Value
Gastric acid secretion	0.00137	HTLV-I infection	0.00362
Calcium signaling pathway	0.00491	Chronic myeloid leukemia	0.00632
Cysteine and methionine metabolism	0.00811	Small cell lung cancer	0.00756
Dopaminergic synapse	0.0129	Prostate cancer	0.00889
Morphine addiction	0.0204	Pathways in cancer	0.0126
Reactome pathway	*p*-Value	Reactome pathway	*p*-Value
CREB phosphorylation through the activation of CaMKII	0.0016	Signaling by NOTCH	0.000159
Ras activation uopn Ca2+ infux through NMDA receptor	0.002	Factors involved in megakaryocyte development	0.000447
Transmission across Chemical Synapses	0.00448	and platelet production	
CREB phosphorylation through the activation of Ras	0.00464	CREB phosphorylation through the activation of CaMKK	0.00798
Trafficking of AMPA receptors	0.00496	AKT phosphorylates targets in the nucleus	0.0093
		CREB phosphorylation	0.0093
GO:BP pathway	*p*-Value	GO:BP pathway	*p*-Value
Second-messenger-mediated signaling	0.00166	Positive regulation of transcription from RNA	3.00e-12
Cellular membrane organization	0.00303	polymerase II promoter	
Skeletal muscle tissue development	0.00309	Regulation of transcription from RNA	3.56e-11
Nervous system development	0.00471	polymerase II promoter	
Cyclic-nucleotide-mediated signaling	0.00546	Transcription from RNA polymerase II promoter	2.65e-10
		Positive regulation of transcription, DNA-dependent	2.74e-10
		Positive regulation of RNA metabolic process	2.74e-10
GO:MF Pathway	*p*-Value	GO:MF Pathway	*p*-Value
Oxygen binding	0.00486	Transcription factor binding	3.95e-12
Protein domain specific binding	0.00522	Transcription from RNA polymerase II promoter	2.29e-10
Voltage-gated calcium channel activity	0.00627	Positive regulation of transcription, DNA-dependent	2.4e-10
Neuropeptide receptor activity	0.00921	Sequence-specific DNA binding	5.92e-9
Peptide receptor activity	0.00931	Negative regulation of transcription, DNA-dependent	6.21e-8
GO:CC Pathway	*p*-Value	GO:CC Pathway	*p*-Value
Endosome	0.00167	Transcription factor complex	8.11e-7
Cytosol	0.0019	Nucleoplasm	0.00000246
Early endosome	0.00232	Nuclear lumen	0.00000296
Membrane-bounded vesicle	0.00638	Nuclear part	0.0000187
Vesicle	0.0111	Organelle lumen	0.0000214

profile were differentially expressed between the two groups. Consistent with our results, miR-148a-3p, and miR-148b-5p showed high expression in PC patients (*p*-values of 2.67e-28 and 7.91e-10, respectively), while miR-24-1 showed low expression (*p*-value of 5.74e-5). These results are shown in Figure 4.

Discussion

miRNAs are small RNA molecules that control gene expression and regulate various biological processes (15). Some microorganisms can influence the gene expression of the host organism and approximately 15% of tumors

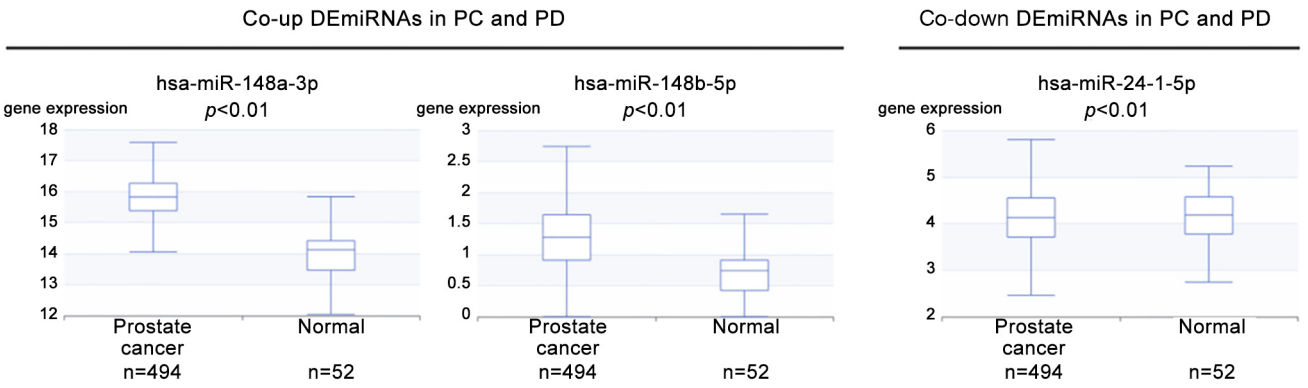

Figure 4. *Analysis of miR-148a-3p, miR-148b-5p, and miR-24-1 in the TCGA prostate adenocarcinoma (PRAD) cohort, stratified based on tumor or control. miRNA levels are shown as log2 expression. p<0.01 using Student's t-test.*

worldwide are linked to microbial infection. Therefore, inflammation is considered a primary risk factor for various cancers (20). Although the mechanisms behind infection-driven PC are unclear, infection and inflammation are known to accelerate PC progression (21). In a study, researchers suggest a link between prostatitis and periodontitis, as bacteria like *P. gingivalis* and *T. denticol*a have been found in both prostate secretions and dental plaques (22). According to a recent study, *P. gingivalis* may increase PD-L1 expression in aggressive primary PC, potentially influencing cancer progression by affecting the tumor microenvironment (23). These studies have shown that there may be some relationships between PD and PC (7-11, 21-23). However, this relationship is not clear, and a definitive cause-and-effect relationship has not been established.

In this study, bioinformatics analyses were used to investigate the regulatory mechanisms mediated by common dysregulated miRNAs in PC and PD. Network analysis was employed to identify key candidate genes and transcription factors that could be affected by the regulatory processes mediated by miRNAs. In addition, functional enrichment analysis on these genes determined the key pathways, molecular functions, and cellular components involved. Furthermore, small molecule compounds associated with Co-DEmiRNA were analyzed, investigating significant linkages between PC and PD.

Oral infections can cause inflammation in distant areas, and persistent inflammation is known to promote carcinogenesis (3). Most of the DEmiRNAs demonstrated a consistent expression pattern in both conditions, which could suggest that the host's oral microenvironment may have similar immune mechanisms that can counteract inflammation or cancer. This similarity in pro-inflammatory and pro-cancer responses might indicate a common dysregulation of miRNA in these two diseases. Therefore, these similar expression patterns may suggest that there is a common miRNA regulatory pathway shared between these two diseases. Among the highest ranked DEmiRNAs, we found that hsa-mir-148a-3p, hsa-mir-148b-5p, and hsa-mir-623 were overexpressed. To further validate our results, we tested them in the TCGA_PRAD cohort, which is independent and representative of a larger group of cases. Independent validation of 494 cases showed that hsa-mir-148a-3p and hsa-mir-148b-5p had significantly higher levels and hsa-mir-24-1 had lower levels in PC patients. These data confirm the results obtained in our study. Hsa-mir-148a and has-mir-148b belong to the miR-148/152 microRNA family, which exhibit differential expression in tumor and non-tumor tissues and are involved in the pathogenesis and progression of diseases. miR-148/152 microRNA family are multifaceted players that influences a wide range of cellular pathways, including cancer development, regulation of immune

responses, and cell fate decision of haematopoietic cells. Various studies have shown that these have oncogenic or tumor suppressor effects by targeting the mRNAs or lncRNAs of different target genes in different types of cancer (24). Fujita and colleagues found that hsa-mir-148a was downregulated in hormone-resistant prostate cancer cells (PC3 and DU145) and overexpression of hsa-mir-148a could inhibit cell growth, cell migration, and invasion by targeting Mitogen and stress-activated kinase 1 (25). In another study, Murata *et al.* found that hsa-mir-148a is overexpressed in LNCaP prostate cells and is an androgen-sensitive microRNA that promotes cell growth by suppressing the expression of its target Cullin-associated and neddylation-dissociated 1, a regulator of ubiquitin ligases (26). These differential expression findings may be explained by the heterogeneity of prostate cancer cells. Other studies have also shown that hsa-miR-148 is associated with geminin and geminin is also associated with prostate cancer (27, 28). There is only one study showing the association of miR148a with periodontitis, a chronic inflammatory disease. In this study, it was determined that the osteogenic potential of stem cells in the periodontitis microenvironment stimulated by *P. gingivalis* lipopolysaccharide was significantly reduced and the level of Neuropilin 1 was decreased while the hsa-mir-148a level increased (29).

To our knowledge, there are few studies demonstrating the effect of hsa-mir-623 on prostate cancer progression. Significant hsa-miR-623 differential expression was found between low-risk and metastatic castration-resistant prostate cancer (30). There was also differential expression of miR-623 in BCR-positive and BCR-negative prostate cancer (31). In addition, miR-623 has been studied in other cancer types, including gastric (32) and pancreatic cancer (33). In addition, miR-623 has been studied in other cancer types, including gastric (28), and pancreatic cancer (29). In gastric cancer, hsa-mir-623 was found to down-regulate cyclin D1 by direct targeting and exhibit tumor suppressor activity (32). In pancreatic cancer, it has been observed that hsa-miR-623 interacts with the matrix metalloproteinase-1 (MMP1) transcript, and there is a negative correlation between hsa-miR-623 expression and MMP1 expression (33). Moreover, it was found that hsa-miR-623 was overexpressed 4.7 times in normal tissues compared to hepatocellular carcinoma tissues, and it was proposed that it may be employed in the prognosis of this malignancy (34). There are also a few studies showing that miR-623 plays an important role in the innate immune responses of human oral epithelial cells against *P. gingivalis*. The first of these is the study showing for the first time that mir-623, along with some other miRNAs, is overexpressed in oral epithelial cells after live bacterial stimulation (35). In another study, mir-623 was found to be overexpressed in the apoptotic process triggered by *P. gingivalis* (36). In a computational analysis study on the role of miRNAs in the acquisition of the oncogenic phenotype in oral submucous fibrosis, which is the activation of pro-inflammatory and fibrogenic cytokines following mucosal damage, mir-623, which is overexpressed in the microenvironment, was identified as a candidate pro-fibrotic miRNA. According to this study, mir-623 may interact with genes, such as *BCAN*, *CYP11B2*, *L2HGDH*, *MAGEB10*, *RAB10*, *RACGAP1*, *RBM28*, *SEZ6L*, *TPPP*, and *ZDHHC20* (37).

Our findings suggest that the primary mechanism connecting PD to PC or other cancer types may include alterations in gene expression controlled by non-coding RNA, notably miRNA. In the Co-DEmiRNA-Gene network, key central genes that could be fundamental between PD and PC include *POU2F1*, *TMOD3*, *SCD*, *PRRC2C*, and *MAT2A*. POU domain, class 2, transcription factor 1 (*POU2F1*, *OCT1*), has been reported to have an oncogenic effect by being overexpressed at both the mRNA and protein levels in various types of cancer, including prostate, bladder, breast, colon, gastric, head and neck cancer (38). Obinata *et al.* found that *POU2F1* overexpression promotes the proliferation and migration of LNCaP prostate cancer cells. They also associated it with poor prognosis in castration-resistant prostate cancer patients (39). In periodontitis, pro-inflammatory cytokines are up-regulated by bacterial activity. Among these, interleukin-6, which is involved in almost every stage of oral inflammatory processes and is the best defined, stands out as one of the targets of

POU2F1 (40). Tropomodulin 3 (*TMOD3*)'s role in tumor cells gaining metastatic properties has been demonstrated in prostate cancer (41, 42), even though there is no study investigating the role of *TMOD3* in periodontitis. Increased expression of stearoyl-CoA desaturase 1 (*SCD1*) has been observed in a wide variety of cancer cells, even prostate cancer, and this condition has been associated with the aggressiveness of the cancer and poor patient prognosis (43). An increase in *SCD1* expression level was detected in a cell line model developed to investigate the chronic effects of tobacco chewing, which is a significant risk factor in the development of oral cancers and head and neck squamous cell carcinoma. It has been noted that this is related to the excessive proliferation of normal oral keratinocytes and their acquisition of an invasive feature (44). An increase in *SCD1* expression was discovered in a study investigating the molecular mechanism involved in hepatic damage in Parkinson's disease, which is known to be closely associated with the emergence and development of various systemic diseases. It was suggested that the disease's development may be related to SCD1/AMPK signal activation (45). Proline-rich coiled-coil 2C (PRRC2C, or KIAA1096), is an important stress granule protein that is part of a wide variety of specialized protein complexes assembled into large membraneless structures that play a role in RNA biogenesis, including the processing, transport, translation, and eventual degradation of mRNA. It has been shown that overexpression of PRRC2C has an effect of increasing the proliferation of cells and promoting metastasis in bladder, lung and liver cancers (46), but no data has been found on its effect in PC and PD. Ding and colleagues investigated m6A methylation-related genes that regulate RNA epitranscriptomics and identified cross-talk genes (*ALKBH5*, *FMR1*, *IGFBP3*, *RBM15B*, *YTHDF1*, *YTHDF2*, and *ZC3H13*) between PC and PD (13). Considering PRRC2C's relationship with RNA biogenesis, it is worth further investigating in terms of PC and PD.

The Co-DEmiRNA-TF network places TP53, CREB1, DNMT1, E2F1, and EGR1 transcription factors at the top (with two miRNA nodes, hsa-mir-148a and hsa-mir-202, in the network). Among these transcription factors, TP53, which is associated with both miRNAs, attracted our attention. Tumor protein 53 (TP53) is a transcription factor (TF) that plays critical roles in cell cycle progression, apoptosis, and DNA damage response pathways (47). Decreases in TP53 protein have been associated with metastatic progression, poor prognosis, and resistance to standard treatments in various types of cancer, including oral squamous cell carcinoma (OSCC), pancreatic cancer, and prostate cancer (47, 48). Research has shown that TP53 affects the proliferation and differentiation of dental stem cells (49). The transcription factor E2F1 plays a role in cell cycle regulation, DNA replication, and cell-matrix interaction. It may also affect cell proliferation, migration, and invasion by acting on the NF-κB pathway in infection, inflammation, and carcinogenesis (50). Network analysis between periodontitis and OSCC by Li *et al.* also showed that TP53 and E2F1 were TFs associated with candidate miRNAs (48).

Concerning the TF cAMP response element binding protein 1 (CREB1), it has been shown to play a critical role in the development and progression of tumors in a wide variety of cancers, including prostate cancer, by responding to various growth factors and stress signals. It has been shown that some miRNAs regulate *CREB1* or, conversely, *CREB1* transcriptionally modulates some miRNAs. In different studies, miR-23a and mir-335 were found to modulate the expression of CREB1 in prostate cancer, while CREB1 was also associated with the expression of miR-27b, miR34b, and miR-181b (51). In a study investigating the integrated miRNA and mRNA expression profile during tension force-induced bone formation in periodontal ligament cells, researchers found several mRNAs, such as CREB1, and several miRNAs different from those we found in our study were identified as hubs of the PPI network (52). Another notable transcription factor, DNA methyltransferase 1 (DNMT1), has been found to be a target of miR-148a-3p in prostate cancer (53, 54). miRNAs targeting DNMT1 or DNMT1 targeting miRNAs in periodontitis have not been reported in the literature. However, one study found that the lncRNA HOTAIRM1 epigenetically regulates HOXA2 via

DNMT1 in human dental follicle stem cells and supports osteogenesis (55). Previous studies have reported overexpression of mir-148a and mir-623 in periodontitis (29, 35, 36). However, no study has demonstrated their relationship with DNMT1.

In this study, small compounds targeted by the shared DEmiRNA were also analyzed. Arsenic trioxide, Gemcitabine, and 1,2,6-TGGP were identified as small-molecule compounds with the strongest correlation. In a study conducted with prostate cancer cells, it was found that arsenic trioxide increased the expression of miR-155 through DNA demethylation. Overexpressed miR-155 was also found to exhibit anti-angiogenic effects by suppressing TGF-beta/SMAD signaling and VEGF expression (56). However, it has been reported that arsenic trioxide, which was once a popular analgesic agent used to necrotize inflamed dental pulp but is not preferred today, can be cytotoxic to both gums and bone and can lead to serious consequences such as jaw osteomyelitis (57). Gemcitabine, which is used in the treatment of many cancers, including bladder, breast, lung, pancreas, and ovarian cancer, has also been shown to have immunomodulatory effects (58). 1,2,6-TGGP, the highest degree and betweenness component in this network, alongside arsenic trioxide and gemcitabine, is a gallotannin with proven activity against a variety of bacteria and diseases (59). In a study investigating the effects of non-coding RNAs in prostate cancer using bioinformatics tools, it was stated that potential drugs such as 1,2,6-TGGP could be a new treatment strategy by modulating lncRNA-mRNA competing relationships (60). In Li and Wang's integrative analysis study, 1,2,6-TGGP was found to be a related compound in periodontitis, *H.pylori*-induced gastric cancer, and *H. pylori*-infected peptic ulcer disease (61). Future research is required to investigate the interactions of these complex chemicals in the context of the link between prostate cancer and periodontitis.

The functional enrichment analysis of Co-DEmiRNA gene and TF networks demonstrated the enrichment of various KEGG pathways associated with cancer. This supports previous findings indicating that periodontitis is a significant risk factor for pancreatic cancer (10, 11). Reactome analyses revealed changes in several pathways related to the NOTCH signaling pathway and CREB phosphorylation, which are associated with the development of periodontitis (62) and play a role in initiating carcinogenesis (51). Among the increasing GO molecular functions among TFs in the network, various functions related to transcription are found. GO BP pathway analysis has implicated pathways involved in both negative and positive regulation of processes, such as RNA metabolism and transcription. Indeed, studies have shown that m6A methylation regulators may be effective in the development of both PC and PD, and that the modulation of these regulators that affect the epitranscriptome causes both transcriptomic and proteomic changes (13, 14, 63).

This research investigated a range of factors, including DEmiRNA, Co-DEmiRNA, TF, and relevant compounds, to explore the interconnected epigenetic mechanisms between PC and PD. One of the significant limitations of the study is the lack of experimental data to confirm potential molecular linkage mechanisms identified through bioinformatic analyses. The absence of experimental validation for the discovered candidate molecular relationships in a laboratory setting can impact the overall reliability of the study and limit the broader evaluation of the findings. This limitation may necessitate prioritizing experimental validation steps in future research or investing more effort in this context. Another crucial point is the potential role of other non-coding RNA types, particularly lncRNAs, circRNAs, and sncRNAs, which were not explored in this study but could play a potentially critical role in the pathogenic mechanism of PC and PD. Therefore, future studies could enrich the overall understanding of PC and PD by more extensively investigating specific linkage mechanisms and interactions of these non-coding RNA types. Future research should utilize various methods, including clinical studies, *in vitro*, and *in vivo* experiments, to identify and validate potential key linkages between Co-DEmiRNA genes, TF pathways, and compounds in the context of PC and PD. These validation processes should involve a detailed and comprehensive examination of biological mechanisms,

particularly contributing to the understanding of inflammation-cancer transformation mechanisms, providing a two-way explanation of interactions between PC and PD. In this context, understanding the roles of genetic, epigenetic, and molecular interactions, along with various biological processes, could be a crucial step in identifying potential therapeutic targets and developing more effective treatment strategies.

Conclusıon

The comprehensive analysis of Co-DEmiRNAs in periodontitis and prostate cancer revealed fundamental genetic molecular mechanisms. These mechanisms are miRNAs, such as hsa-mir-148b-3p, hsa-mir-148a-3p, hsa-mir-623, and hsa-mir-202, genes including *POU2F1*, *TMOD3*, *SCD*, *PRRC2C*, and *MAT2A*, and transcription factors, such as TP53, CREB1, DNMT1, E2F1, and EGR1. In addition, the study highlighted small-molecule compounds like Arsenic trioxide, Gemcitabine, and 1,2,6-Tri-O-galloyl-beta-D-glucopyranose most associated with DEmiRNAs. The identified core Co-DEmiRNAs in this study could serve as an effective guide in understanding the processes of transformation between inflammation and cancer and provide valuable insights for future research.

Data Availability

Publicly available datasets were analyzed in this study and can be found at: https://www.ncbi.nlm.nih.gov/geo/ and https://www.cancer.gov/tcga [Last accessed on July 1, 2024). Data generated by the Authors are shown in this paper or in the Supplementary Materials. Further data are available from the corresponding author upon reasonable request.

Supplementary Material

Supplementary Table I available at: https://doi.org/10.6084/m9.figshare.27376707.v1; Supplementary Table II available at: https://doi.org/10.6084/m9.figshare.27376713; Supplementary Table III available at: https://doi.org/10.6084/m9.figshare.27376; Supplementary Table IV: https://doi.org/10.6084/m9.figshare.27376704

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

Conceptualization, A.K., D.S.A.; methodology, A.K., N.K.S. and C.U.; software, C.U., N.K.S., validation, A.K., D.S.A.; formal analysis: A.K., G.A.; investigation, A.K., D.S.A.; resources, A.K., N.K.S.; data curation, N.K.S., C.U.; data acquisition, N.K.S., C.U.; writing original draft preparation, A.K.; writing review and editing, A.K., G.A. and M.K.; visualization, A.K., D.S.A.; supervision, M.K. All Authors have read and agreed to the published version of the manuscript.

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