



Investigating the Role of SPAG4 in Chronic Periodontitis Based on Bioinformatics and Histological Evidence

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Abstract: Objective: This study employs bioinformatics strategies to analyze the potential role of SPAG4 in the progression of chronic periodontitis and validates these findings through experiments using clinical samples, with the aim of providing new insights for the screening of biomarkers for early diagnosis and targeted interventions for this disease. **Methods:** The periodontitis transcriptomic dataset GSE10334 was obtained from the GEO database, and bioinformatics analysis was performed to elucidate the expression profile of SPAG4. Gingival tissue samples were collected from healthy controls and patients with chronic periodontitis; RT-qPCR was used to detect differences in SPAG4 mRNA expression, and immunohistochemistry was employed to reveal its protein distribution. **Results:** Bioinformatics analysis revealed that SPAG4 expression was significantly upregulated in chronic periodontitis tissues, with an area under the receiver operating characteristic (ROC) curve (AUC) of 0.868. A protein interaction network was constructed using the STRING database and Cytoscape software, identifying four core immune-related genes: TNFRSF17, CD79A, CD19, and CD79B. Clinical validation results indicated that, compared with the healthy control group, the mRNA levels of both SPAG4 and CD79A were significantly elevated in chronic periodontitis tissues ($P < 0.05$); Spearman's correlation analysis confirmed a positive correlation between their expressions ($r = 0.452$, $P = 0.019$). Immunohistochemical results showed that SPAG4-positive signals were primarily localized in the gingival epithelial layer. **Conclusion:** SPAG4 may serve as a diagnostic biomarker and a potential therapeutic target for chronic periodontitis.

Keywords: SPAG4; CD79A; Chronic Periodontitis; Immune Infiltration; Inflammatory Response

1 Introduction

Chronic periodontitis is a chronic inflammatory disease characterized by impaired inflammation-mediated tissue repair and an imbalance in immune homeostasis, with a high global prevalence[1]. The disease activates host immune cells, inducing the release of various pro-inflammatory cytokines[2], which in turn leads to bone resorption and damage to periodontal tissues. Currently, clinical treatment primarily involves a combination of mechanical therapy and antimicrobial agents; however, this approach is limited by bacterial resistance and insufficient plaque removal efficacy[3]. Therefore, identifying molecular biomarkers of periodontitis and pinpointing intervention targets are crucial for diagnosis and prognosis[4].

Sperm-associated antigen 4 (SPAG4) belongs to the classic SUN gene family[5]. Using qRT-PCR, Gao et al. compared samples from six patients with periodontitis with those from healthy controls and confirmed that SPAG4 is significantly overexpressed in the gingival tissue of patients, suggesting that it may be involved in the pathogenesis of periodontitis[6]. Given that existing studies are largely limited to bioinformatics-based predictions or validation using small sample sizes, this study investigates the role of SPAG4 in chronic periodontitis based on bioinformatics and histological evidence, to provide new insights for the screening of biomarkers for early diagnosis and targeted interventions for this disease.

2 Materials and Methods

2.1 Acquisition of Gene Chip Datasets

Using the search term "periodontitis" in the GEO database of <https://www.ncbi.nlm.nih.gov/geo/> (NCBI), we retrieved dataset GSE10334[7], with platform ID GPL570. The microarray data were derived from 247 samples (64 healthy gingival tissue samples and 183 periodontitis tissue samples). The relevant microarray data from the dataset were downloaded and analyzed.

2.2 Single-Gene Variation Analysis and Screening for Immune-Related Molecules

Differential expression analysis was performed based on the median expression levels of SPAG4 in periodontitis tissue, using the screening criteria $|\log_2FC| \geq 0.5$ and $P < 0.05$. Volcano plots and heatmaps were generated using the GOplot



package and ggplot2 in R. The intersection of the identified differentially expressed molecules and the immune-related molecules downloaded from the IMMPort database was calculated, and a Venn diagram was plotted.

2.3 Function Enrichment Analysis

Function enrichment analysis includes Gene Ontology (GO) functional annotation analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. To investigate the functions of differentially expressed genes and their roles in biological processes, the GOpot package and ggplot2 in R were used to perform functional enrichment analysis and visualization of the identified differentially expressed molecules.

2.4 Constructing a protein-protein interaction network (PPI) and screening for core immune-related genes

Using the online STRING database to construct a protein-protein interaction (PPI) network, import the network into Cytoscape, and use the CytoHubba plugin to screen for and visualize core genes from the PPI network; then, identify the intersection of these genes and the differentially expressed immune-related genes to obtain the top four core genes associated with periodontitis.

2.5 Sample Collection

Patients with chronic periodontitis who visited the outpatient department of the Department of Dentistry at XX Hospital between June 2022 and December 2023 and met the inclusion criteria were selected as the observation group, while patients with healthy gums served as the control group. All participants voluntarily enrolled in the study and provided informed consent.

1) Inclusion Criteria for the Periodontitis Group: Subjects met the diagnostic criteria of the 2018 New International Classification of Periodontal and Implant-Related Diseases[8]

Inclusion criteria for the healthy control group: BOP-positive sites < 10%, no loss of attachment or alveolar bone resorption, periodontal probing depth (PD) ≤ 3 mm, and no systemic diseases associated with periodontitis, such as hypertension or diabetes.

2) Exclusion criteria: Use of anti-inflammatory medications such as antibiotics and steroids within the past three months; concurrent severe oral diseases such as tonsillitis or pharyngitis; concurrent severe systemic diseases; and women who are pregnant, menstruating, or breastfeeding. This study was reviewed and approved by the Ethics Committee (Ethics Review No.: 2022053002).

2.6 Major Reagents and Instruments

HC-2518R high-speed refrigerated centrifuge, microplate reader and analyzer software (Thermo, USA), and quantitative PCR instrument (Biosyn LightCycler 96, USA). The primers were synthesized by Nanning Kedi Biotechnology Co., Ltd.

2.7 mRNA Extraction from Chronic Periodontitis and Healthy Gingival Tissue and Real-Time Fluorescent Quantitative PCR (qRT-PCR)

The collected samples were ground at low temperature, and total RNA was extracted using the standard TRIzol method, followed by reverse transcription into cDNA. PCR amplification was performed using the cDNA as a template. The reaction protocol was as follows: (1) Pre-denaturation: 95°C, 60 s, 1 cycle; (2) Amplification: 95°C, 5 s; 60°C, 60 s, 40 cycles; (3) Melting curve analysis: 95°C, 10 s; 65°C, 60 s; 97°C, 1 s. GAPDH was used as an internal control, and statistical analysis was performed using the 2^{-ΔΔCt} method. Primer sequences are shown in Table 1.

Table 1: PCR primers

Gene	Forward (5'→3')	Reverse (5'→3')
GAPDH	GCACCGTCAAGGCTGAGAAC	TGGTGAAGACGCCAGTGGGA
SPAG4	CCACAAGGAGGTGTCCACTGTT	CGTGGGATGTCTTCTGCAGGT
CD79A	GGCACCAAGAACCGAATCATC	TCATACATGGAGCAGTCGTCCAG

2.8 Detection of SPAG4 Protein Expression Levels in Gingival Tissue from Patients with Chronic Periodontitis Using Immunohistochemistry

The collected samples were subjected to routine dehydration, clearing, paraffin embedding, and serial sectioning. Endogenous peroxidase was blocked, followed by the addition of SPAG4 primary antibody and incubation overnight at 4°C. Subsequently, HRP-labeled secondary antibody was added and incubated at room temperature. The sections were then dehydrated and mounted. Scans were performed using a panoramic scanner, and three randomly selected fields of view were photographed under a light microscope for optical density analysis. Brownish-yellow staining in the cell nucleus or cytoplasm was considered positive expression.

2.9 Statistical Analysis

Analysis was performed using SPSS 27.0 and GraphPad Prism 8.0 software. A two-sample rank-sum test was used to compare the relative expression levels of SPAG4 and CD79A mRNA in chronic periodontitis tissue and healthy gingival tissue. Spearman's correlation coefficient was used to analyze the correlation between the expression levels of SPAG4 and CD79A in chronic periodontitis tissue, with P < 0.05 considered statistically significant.

3 Results

3.1 Expression of SPAG4 in Chronic Periodontitis Tissue

SPAG4 expression was significantly higher in periodontitis tissue than in healthy gingival tissue, with a statistically significant difference (P < 0.001) (Figure 3-1A). A ROC curve was plotted based on SPAG4 expression in periodontitis tissue and healthy gingival tissue; the results showed an AUC of 0.868 (Figure 3-1B).

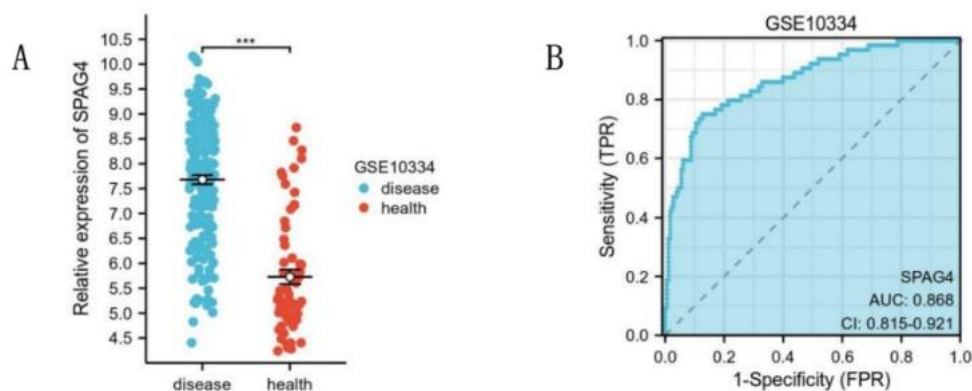


Figure 3-1 SPAG4 expression and diagnostic ROC analysis in periodontitis group and healthy gingival group

(A) Comparison of SPAG4 expression in periodontitis group and healthy gingival group

(B) Diagnostic ROC analysis

3.2 Results of SPAG4 Single-Gene Variation Analysis and GO/KEGG Functional Enrichment Analysis

Single-gene differential analysis identified 553 differentially expressed molecules, of which 360 were upregulated and 193 were downregulated (Figure 3-2A). The results of the GO enrichment analysis showed that, in terms of biological processes, the differentially expressed molecules were primarily involved in B cell receptor signaling pathway, immune response-regulating signaling pathway, immune response-activating cell surface receptor signaling pathway; in terms of cellular components, they were mainly localized in level-3 granules, endoplasmic reticulum protein complexes, endoplasmic reticulum chaperone complexes, and cornified envelope; and in terms of molecular functions, they were primarily involved in misfolded protein binding and IgG binding. The results of the KEGG enrichment analysis showed that the differentially expressed molecules were primarily enriched in pathways related to protein processing in the endoplasmic reticulum and leukocyte transendothelial migration (Figure 3-2B). By intersecting the set of differentially expressed molecules with that of immune-related molecules, 63 differentially expressed immune-related genes (IRDEGs) were identified (Figure 3-2C).

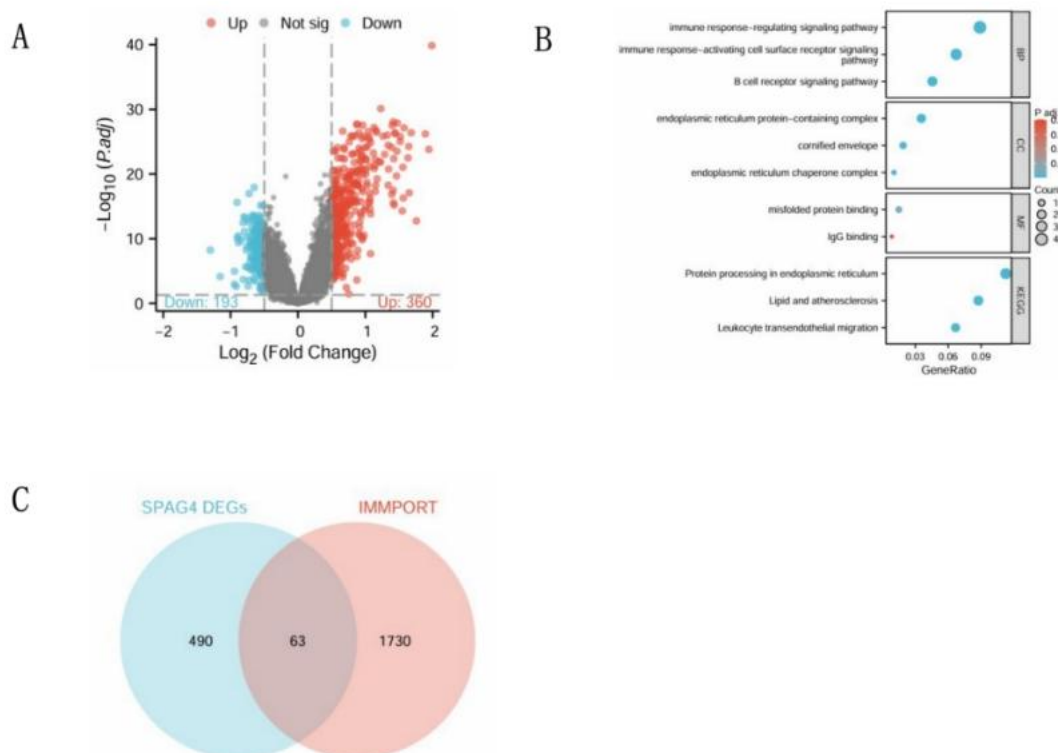


Figure 3-2 SPAG4 single gene difference analysis and screening of immune-related molecules

(A) SPAG4 single gene differential expression molecular volcano map (blue for down-regulated molecules, red for up-regulated molecules)

(B) GO/KEGG analysis results of SPAG4 single gene differential molecules

(C) Intersection Venn diagram of SPAG4 single gene differential expression molecules and IMMPORT immune molecules

3.3 Results of PPI Network Construction and Core Gene Screening

By constructing a PPI network, a total of 10 core genes were identified (Fig. 3-3A, B). By taking the intersection of these genes with differentially expressed immune-related genes (IRDEGs), four core immune-related genes were identified: TNFRSF17, CD79A, CD19, and CD79B (Fig. 3-3C). Furthermore, in dataset GSE10334, CD79A showed a certain degree of correlation with SPAG4 (Fig. 3-3D).

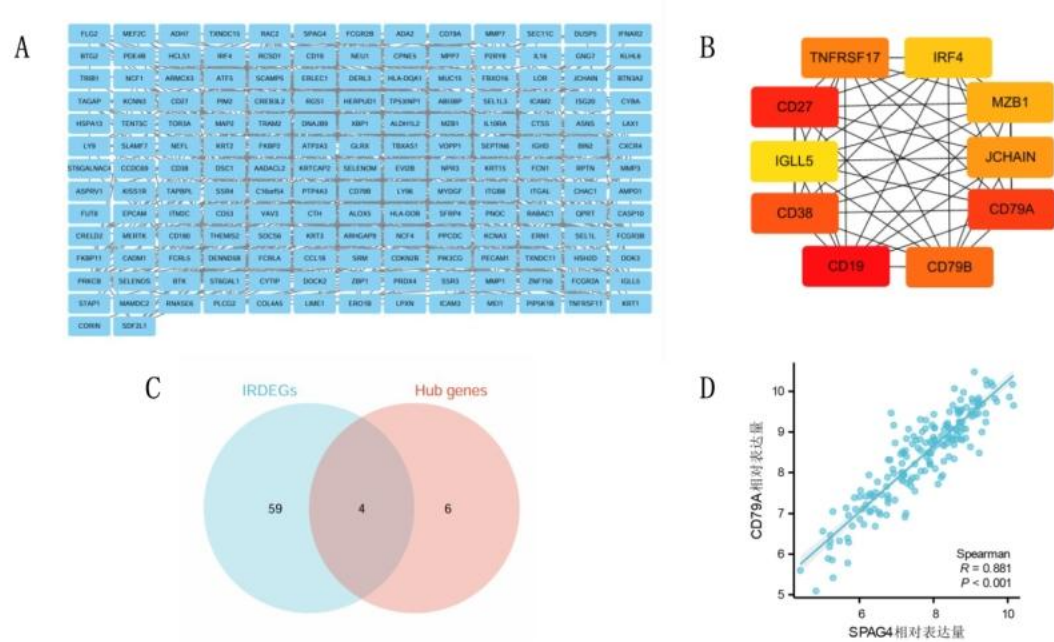


Figure 3-3 SPAG4 single gene differential expression molecular protein-protein interaction network and immune-related core molecule screening
(A) SPAG4 single gene differential expression molecular protein interaction network (B) CytoHubba screening core genes
(C) Immune-related core molecule screening

3.4 Results of qRT-PCR Assays for SPAG4 and CD79A mRNA and Analysis of Correlations

3.4.1 Differences in SPAG4 mRNA Expression Between Tissue from Patients with Chronic Periodontitis and Healthy Gingival Tissue

The two sets of data did not follow a normal distribution and are expressed as “M(Q25, Q75).” Analysis using the two-sample rank-sum test revealed that the relative expression level of SPAG4 mRNA in chronic periodontitis tissue was higher than that in healthy gingival tissue, and the difference was statistically significant ($P < 0.001$) (Figure 3-4A, Table 2). The area under the ROC curve (AUC) for diagnostic analysis was 0.864 (Figure 3-4B).

Table 2 Comparison of the expression levels of SPAG4 in chronic periodontitis and normal gingival tissues

Category	Number of Examples	M(P ₂₅ , P ₇₅)	U-Value	P-Value
Periodontitis Group	34cases	7.235(3.302, 19.643)	116	4.36e-07
Healthy Gingival Group	25cases	0.860(0.493, 1.511)		

3.4.2 Differences in CD79A mRNA Expression Between Tissue from Patients with Chronic Periodontitis and Healthy Gingival Tissue

Two sets of data did not follow a normal distribution and are denoted as “M(Q25, Q75).” Analysis using the two-sample rank-sum test revealed that the relative expression level of CD79A mRNA in chronic periodontitis tissue was higher than that in the healthy gingiva group, and the difference was statistically significant ($P < 0.001$) (Fig. 3-4C, Table 3).

Table 3 Comparison of the expression levels of CD79A mRNA in chronic periodontitis and normal gingival tissues

Category	Number of Examples	M(P ₂₅ , P ₇₅)	U-Value	P-Value
Periodontitis Group	35 cases	11.784(4.852, 27.810)	69	9.08e-10
Healthy Gingival Group	25 cases	1.156(0.182, 2.674)		

3.4.3 Correlation Between Relative Expression Levels of SPAG4 and CD79A in Tissue Samples from Patients with Chronic Periodontitis

The relationship between the expression of SPAG4 and CD79A mRNA in chronic periodontitis tissues was analyzed using Spearman’s correlation coefficient. The results showed that the expression of SPAG4 and CD79A mRNA in

chronic periodontitis tissues was positively correlated ($r = 0.452$, $P = 0.019$), and the difference was statistically significant ($P < 0.05$) (Fig. 3-4D).

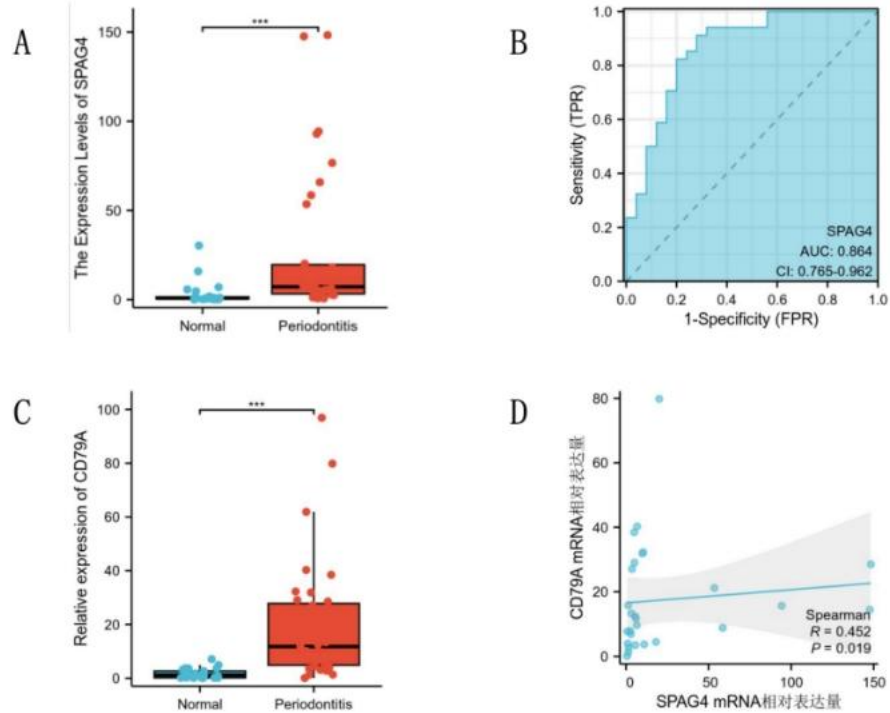


Figure 3-4 Comparison and correlation analysis of the relative expression levels of SPAG4 and CD79A in chronic periodontitis tissue and healthy gum tissue

(A) Comparison of the relative expression levels of SPAG4 in chronic periodontitis tissue and healthy gum tissue * $P < 0.001$

(B) Diagnostic ROC analysis

(C) Comparison of CD79A relative expression level in chronic periodontitis tissues and healthy gingival tissues ** $P < 0.001$

(D) Correlation analysis between SPAG4 expression level and CD79A relative expression level in chronic periodontitis tissues

3.5 SPAG4 Immunohistochemical Staining Results

Immunohistochemical analysis revealed that the SPAG4 protein is primarily distributed in the epithelial layer of the gingiva, with staining observed on the cell membranes and in the cytoplasm; positive staining appears yellow or yellowish-brown. SPAG4 staining was also observed in inflammatory cells and vascular endothelial cells. The immunohistochemical staining results are shown below (Figures 3-5).

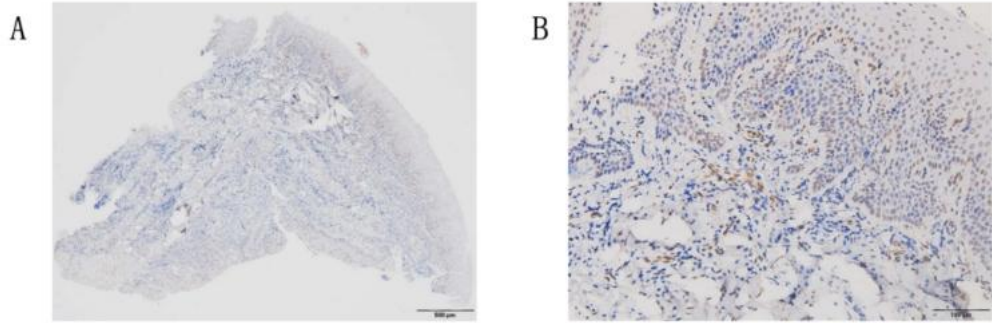


Figure3-5 SPAG4 immunohistochemical staining results
(A. x4 Mmagnification; B. x20 Magnification)

4 Discussion

Periodontitis is a chronic infectious disease. Studies have shown[9] that the development of periodontitis is associated with subgingival plaque triggering an excessive immune inflammatory response in the body, which in turn affects the course of the disease and exacerbates its clinical symptoms.

SPAG4 was initially discovered in studies related to sperm. Recent research[10], based on periodontitis microarray and RNA-seq datasets, identified key genes associated with periodontitis (DERL3, FKBP11, LAX1, CD27, SPAG4,

ST6GAL1, MZB1, SEL1L3) by intersecting the results of differential gene expression analysis and WGCNA. Furthermore, CIBERSORT analysis was used to determine changes in the proportions of immune cells in periodontitis and healthy gingival tissues. Correlation analysis revealed that the expression of key periodontitis genes was highly positively correlated with changes in the proportion of plasma cells and highly negatively correlated with changes in the proportions of memory B cells and resting dendritic cells.

Currently, most studies on SPAG4 and periodontitis have been database analyses, which only suggest that SPAG4 may be involved in the immune response to periodontitis. At the same time, existing research has failed to elucidate the specific role of SPAG4 in the immune process of periodontitis, and the association between the two remains unclear. With the advancement of high-throughput technologies, bioinformatics techniques have been widely applied in the field of medical research. In this study, analysis of the GSE10334 dataset revealed that SPAG4 is highly expressed in gingival tissue affected by periodontitis, which is consistent with the findings of Gao et al.[10]. Subsequently, the expression levels of SPAG4 were measured in six cases of clinical periodontitis and healthy gingival tissue, yielding identical results, suggesting that SPAG4 may play a role as a key factor in periodontitis. Furthermore, the ROC results in this study showed an AUC of 0.868, suggesting that SPAG4 has potential diagnostic value in distinguishing between periodontitis and healthy gingival tissue. Functional enrichment analysis revealed that SPAG4 is primarily involved in B-cell activation, B-cell immune responses, and stimulation responses. This finding is consistent with the characteristic of abnormal B-cell activation observed in the local immune environment of patients with periodontitis[11], [12]. Consequently, it is hypothesized that SPAG4 may exert an immunoregulatory role in periodontitis by influencing B-cell activation and the activation of B-cell receptor signaling pathways.

qRT-PCR experiments revealed that SPAG4 is expressed in both periodontitis and healthy tissues, with significantly higher expression levels in periodontitis tissues. Combined with the findings of previous studies, these results suggest that SPAG4 plays a role in the immune response of hosts with periodontitis.

CD79A is primarily expressed on the surface of B lymphocytes and B-cell tumors and binds to immunoglobulins noncovalently with CD79B[13]. Studies have confirmed that it plays a crucial role in B-cell signal transduction[14]. In this study, four key immune genes associated with periodontitis—namely, TNFRSF17, CD79A, CD19, and CD79B—were identified through the construction of a protein interaction network. qRT-PCR results showed that CD79A mRNA expression levels were higher in chronic periodontitis tissue than in healthy gingival tissue, which is consistent with the findings of previous studies and suggests that CD79A may be involved in the development and progression of periodontitis. Based on the biological characteristics of SPAG4, studies have shown[15] that mutations in the CD79A gene are one of the causes of autosomal recessive agammaglobulinemia (ARA), indicating that this gene is involved in the development of primary immunodeficiency disorders, as well as the onset and progression of autoimmune diseases such as systemic lupus erythematosus and autoimmune hepatitis. We hypothesize that CD79A is involved in the host immune response to periodontitis and may play an important role in this process. In this study, we conducted a correlation analysis of the expression levels of SPAG4 and CD79A mRNA in periodontitis tissue. The results showed a positive correlation between the two ($r = 0.452$, $P = 0.019$), suggesting that SPAG4 and CD79A may influence each other's expression in the host immune response to periodontitis.

In this study, immunohistochemical staining results showed that the SPAG4 protein was primarily distributed in the gingival epithelium, with staining observed in the cell membrane and cytoplasm; SPAG4 staining was also visible in inflammatory cells and vascular endothelial cells. Research has shown[16] that the gingival epithelium serves as the first line of defense for periodontal tissues against invasion by external pathogens, as well as the first line of defense for the body's immune system. Upon bacterial invasion, immune cells in the epithelial layer phagocytose and kill bacteria by releasing inflammatory and immune factors, playing a crucial role in the onset and progression of periodontitis. Therefore, we hypothesize that during the inflammatory phase of periodontitis, the activation of the host immune response leads to increased secretion of the SPAG4 protein, which plays a role in the immune response associated with periodontitis.

In summary, SPAG4 is expressed at higher levels in chronic periodontitis tissue than in healthy gingival tissue, suggesting that SPAG4 may be involved in the development and progression of chronic periodontitis. Based on the ROC analysis results from this study, it is hypothesized that SPAG4 may serve as a biomarker for the diagnosis and prognosis of periodontitis, as well as a potential therapeutic target; SPAG4 showed a positive correlation with CD79A mRNA, suggesting that SPAG4 and CD79A may have a regulatory relationship and jointly participate in modulating the host's immune response to periodontitis; however, this requires further confirmation through *in vivo* and *in vitro* experiments. The findings of this study may provide a theoretical basis and potential immunotherapeutic targets for further exploration of the molecular mechanisms underlying the pathogenesis and progression of periodontitis involving SPAG4.

5 Conclusion

Differences in SPAG4 expression between chronic periodontitis and healthy gingival tissue, along with its positive correlation with CD79A mRNA expression in chronic periodontitis tissue, suggest that SPAG4 may serve as a diagnostic biomarker and a potential therapeutic target for chronic periodontitis. Future research should explore the molecular mechanisms underlying SPAG4's role in the pathogenesis and progression of chronic periodontitis, as well as its potential as an immunotherapeutic target, to provide new insights for targeted interventions in chronic periodontitis.

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Ethics approval and consent to participate

This work was reviewed and approved by the Ethics Committee of Youjiang Medical University For Nationalities (Ethics Review No.: 2022053002).

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