Clinical, Cosmetic and Investigational Dermatology

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ORIGINAL RESEARCH

Identification of Oxidative Stress-Related Shared Biomarkers in Vitiligo and Periodontitis: A Bioinformatics and Machine Learning Study

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Background: Oxidative stress is associated with both vitiligo and periodontitis, but the detailed pathogenesis requires further elucidation. Evidence suggests a connection between periodontitis and autoimmune as well as chronic inflammatory skin diseases. The objective of this study is to investigate shared biomarkers related to oxidative stress in periodontitis and vitiligo using an integrated approach of bioinformatics and machine learning.

Methods: Data for periodontitis and vitiligo were downloaded from the NCBI GEO public database. After batch effect removal, differentially expressed genes (DEGs) were identified and combined with weighted gene co-expression network analysis (WGCNA) to pinpoint shared genes. Pathway enrichment analysis using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) was conducted for the shared genes. We identified hub genes with least absolute shrinkage and selection operator (LASSO) regression and Support Vector Machine (SVM) machine learning algorithms. Finally, the ssGSEA method was used to analyze the level of immune cell infiltration.

Results: Ninety-three shared genes between periodontitis and vitiligo were identified, with GO and KEGG enrichment analyses revealing a significant association with oxidative stress. Through machine learning algorithms, PTGS2, CCL5, and PRDX4 were identified as hub genes serving as shared biomarkers for oxidative stress in both diseases. Furthermore, immune cell infiltration revealed that periodontitis and vitiligo share similar immune infiltration patterns.

Conclusion: Our study has identified PTGS2, CCL5, and PRDX4 as key biomarkers for vitiligo and periodontitis, two diseases linked by similar immune infiltration patterns. These biomarkers offer new diagnostic insights and potential therapeutic targets.

Keywords: vitiligo, periodontitis, oxidative stress, bioinformatics, machine learning, immune cell infiltration

Introduction

Periodontitis is a chronic multifactorial inflammatory disease associated with the accumulation of dental plaque, primarily characterized by the progressive and irreversible destruction of periodontal ligament and alveolar bone.[1,2] Globally, approximately 743 million people suffer from severe periodontitis, accounting for about 11% of the world's population.[3] Oxidative stress is one of the crucial pathophysiological mechanisms in periodontitis. The accumulation of dental plaque and oral microbial dysbiosis in periodontitis lead to the release of proinflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α), which stimulate the production of reactive oxygen species (ROS). The imbalance between the increased oxidative burden due to excessive ROS and the insufficiently increased antioxidant defense capacity results in oxidative stress in the affected tissues.[4–6]

Received: 9 June 2025
Accepted: 1 October 2025
Published: 23 October 2025

Vitiligo is a chronic skin depigmentation disorder and autoimmune disease associated with the selective destruction of melanocytes, primarily presenting with white patches on the skin.[7] Approximately 0.5% to 1% of the global population suffers from vitiligo.[8] Its pathogenesis is multifactorial, involving an interplay of genetic susceptibility, oxidative stress, and a dysregulated immune response that culminates in the destruction of melanocytes by $CD8^+$ T cells.[9,10] Oxidative stress is crucial in activating the autoimmune responses associated with vitiligo. Melanocytes produce high levels of ROS as byproducts during melanin synthesis. The accumulation of ROS leads to the destruction and dysfunction of melanocytes through various pathways, including endoplasmic reticulum stress, mitochondrial dysfunction, lipid peroxidation, and adhesion defects, while also activating the body's innate and adaptive immune responses,[11,12] ultimately triggering the onset of vitiligo.

It has been proposed that oral melanocytes may prevent oxidative stress by scavenging free radicals, while vitiligo patients with an absence of melanin pigmentation demonstrate increased gingival inflammation.[13] Furthermore, periodontitis has been linked to several autoimmune and chronic inflammatory skin diseases, including psoriasis, alopecia areata, and atopic dermatitis. The study indicated that periodontitis activated innate and adaptive immune responses by inducing the upregulation of cytokines IL-6 and IL-17A, thereby increasing the proliferation of keratinocytes and the loss of differentiation, leading to the onset of psoriasis.[14] Patients with periodontitis were at a significantly increased risk of developing psoriasis.[15] Additionally, the inflammatory process of periodontitis, the imbalance of Th17/Treg cells, and the upregulation of pro-inflammatory cytokines (IFN-γ, IL-1β, and IL-17) have also been demonstrated in alopecia areata. A cohort study in a Korean population revealed a significantly increased risk of alopecia areata in patients with periodontitis.[16] Inflammatory responses resulting from the imbalance of Th1, Th2, Th17, and Treg cells play a critical role in the progression of periodontitis,[17] similarly, atopic dermatitis can be partially explained by the imbalance of Th1, Th2, Th17/23, and Th22 cells in response to epithelial microbial dysbiosis.[18] Two cross-sectional surveys found a significant correlation between atopic dermatitis and periodontitis.

Therefore, we suppose that there may be a correlation between periodontitis and vitiligo, with oxidative stress potentially playing a common role in the molecular mechanisms of both diseases. This study employed an integrated bioinformatics and machine learning to identify shared oxidative stress-related biomarkers, providing novel insights for early diagnosis, facilitating interdisciplinary patient management, and revealing potential therapeutic targets.

Methods

Transcriptome Data Processing

The transcriptome datasets GSE65127, GSE75819 (vitiligo), and GSE16134 (periodontitis) were downloaded from the NCBI GEO public database. All analyses for this study were conducted between January and October 2024. The dataset for vitiligo was a combination of GSE65127 and GSE75819, which included 25 vitiligo samples and 25 healthy controls. The dataset for periodontitis was from GSE16134, which included 241 periodontitis samples and 69 healthy controls. The "sva" package was utilized to identify and construct surrogate variables for high-dimensional data, thereby eliminating batch effects. Principal component analysis plots were generated using the "FactoMineR" and "factoextra" packages for visualization. The "preprocessCore" package's normalize.quantiles function was applied to normalize the expression matrix based on quantiles, reducing the impact of sequencing depth and gene length, and minimizing errors due to microarray technology. Differentially expressed genes (DEGs) were identified using the "limma" package,[19] with significance thresholds set at an adjusted p-value < 0.05 and $|\text{LogFC}| > 0.585$. Finally, the "ggvenn" package was used to create a Venn diagram to identify overlapping DEGs for subsequent analysis.

Construction of Co-Expression Networks Using WGCNA

Weighted gene co-expression network analysis (WGCNA) is one of the most important and widely applied systems biology informatics methods, which groups genes into modules based on their co-expression similarity across samples to describe patterns of inter-gene correlation.[20] Co-expression networks were constructed for the periodontitis and vitiligo datasets using the "WGCNA" package, with the top 50% of genes by variance being included in the input matrix. The optimal soft-thresholding power was determined using the pickSoftThreshold function. The correlation matrix was

transformed into an adjacency matrix, then converted into a Topological Overlap Matrix (TOM). Then a hierarchical clustering tree was constructed and a dynamic tree cut algorithm (minModuleSize = 30) was applied to identify distinct gene modules. Modules were classified using an average linkage hierarchical clustering method based on the TOM, to group genes with similar expression patterns into gene modules. Finally, the Pearson correlation was used to calculate the relationship between the merged modules and disease status. In both periodontitis and vitiligo datasets, the blue module exhibited the strongest positive correlation and was selected for subsequent analysis.

GO and KEGG Functional Enrichment Analysis

By integrating the DEGs and the module genes identified through WGCNA, we identified shared genes in periodontitis and vitiligo. The "clusterProfiler" package and the Metascape online tool were used to conduct GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analyses on the shared genes to elucidate the biological functions and signaling pathways involved in the diseases.[21] Enrichment was considered statistically significant when the p-value < 0.05.

Identification of Candidate Genes

We filtered oxidative stress-related genes from the GeneCards database with a Relevance score cutoff of 10, resulting in 916 genes. Using the "ggvenn" package, we created a Venn diagram to identify overlapping genes between shared genes and oxidative stress-related genes as candidate genes. Moreover, we established protein-protein interaction (PPI) networks for candidate genes using the STRING database and visualized it with Cytoscape software, applying the MCC algorithm to assess gene relevance.

Screening Hub Genes by Machine Learning

Least absolute shrinkage and selection operator (LASSO) regression and support vector machine (SVM) machine learning algorithms were used to screen hub genes. The dataset of 10 candidate genes for periodontitis and vitiligo was input into the LASSO regression separately, and a regression model was constructed using the "glmnet" package. We performed 5-fold cross-validation, setting the "family" parameter in the function to "binomial". Log (lambda) curves of the LASSO coefficients were plotted for the 10 features. Subsequently, the SVM algorithm from the "e1071" package and "MSVM-RFE" package was applied to model the 10 candidate genes, using sequential backward feature elimination method to determine the optimal hub genes. This process included 10-fold cross-validation, and the results were visualized, with red circles indicating the maximum classification accuracy. The corresponding gene set represented the most accurate diagnostic biomarkers at the lowest 5-fold cross-validation error. Finally, a Venn diagram was drawn using the "ggvenn" package to retain the overlapping genes identified by the LASSO and SVM methods in different datasets as the hub genes.

Diagnostic Efficacy and Predictive Value of Hub Genes

Boxplots were generated using the "ggpubr" package to visualize the expression levels of the four shared hub genes in both the periodontitis and vitiligo datasets. The genes that were commonly upregulated or downregulated in both diseases were chosen. The gene TXN, which was downregulated in periodontitis but upregulated in vitiligo, was excluded from the analysis. Ultimately, three hub genes (PTGS2, CCL5, and PRDX4) were identified. To assess the predictive and discriminative capabilities of these three hub genes, we plotted the receiver operating characteristic (ROC) curves and calculated area under the curve (AUC) values using the "pROC" package.

Construction of Regulatory Networks and Prediction of Potential Drugs

By accessing the TRRUST database (https://www.grnpedia.org/trrust/) and the miRWalk database (http://mirwalk.umm.uni-heidelberg.de), we predicted transcription factors (TFs) and miRNAs.[22,23] MiRNAs that are associated with at least two hub genes were selected. Potential drugs related to the hub genes were screened using the DSigDB database from the Enrichr platform. Finally, a visual network was constructed using Cytoscape software.

Analysis of Immune Cell Infiltration

To characterize the immune cell infiltration landscape in periodontitis and vitiligo, we conducted ssGSEA analysis using the "GSVA" package. The ssGSEA method estimates the differences in infiltration abundance composition of 28 immune cell types between two groups based on matrix gene expression data. Spearman correlation analysis was used to reveal the correlation between hub genes and immune cell distribution. The results were visualized using the "ggpubr" and "pheatmap" packages.

Statistical Analysis

All statistical analyses were performed using R software (Version 4.4.0). The significance of fold changes in the microarray data was assessed using t-tests. Spearman correlation analysis was employed to evaluate the association between genes and immune cells. Statistical significance was set at a p-value < 0.05.

Results

Elimination of Batch Effects and Identification of DEGs

The flowchart of the study is presented in Figure 1. Before conducting bioinformatics analysis, we identified significant batch effects in the two vitiligo datasets (GSE65127 and GSE75819) (Supplementary Figure 1A). After eliminating the batch effects in the vitiligo datasets using the "sva" package, we obtained reliable results for subsequent analysis (Supplementary Figure 1B). In total, we identified 1121 DEGs in periodontitis and 847 DEGs in vitiligo. The volcano plots displayed 729 upregulated and 392 downregulated DEGs in periodontitis (Figure 2A), as well as 533 upregulated and 314 downregulated DEGs in vitiligo (Figure 2B). The heatmaps separately depicted the top 20 most significantly upregulated and downregulated genes in periodontitis and vitiligo (Figure 2C and D), showing marked differences in the expression of these top 20 genes between the control and disease groups. Finally, a Venn diagram was drawn to identify 58 overlapping DEGs (Figure 2E). The list of overlapping DEGs can be found in Supplementary Table 1.

WGCNA Network Construction and Module Identification

We performed WGCNA on the periodontitis and vitiligo datasets separately to explore the correlation between clinical characteristics and genes, checking for outliers through sample clustering and removing any outlier samples. To ensure the construction of scale-free networks, we calculated the scale-free topology fit index and average connectivity. The "pickSoftThreshold" package determined the optimal soft threshold to be 16 for the periodontitis dataset and 24 for the vitiligo dataset (Figure 3A and B). A total of 8 modules were identified in the periodontitis dataset, and 6 modules were identified in the vitiligo dataset (Figure 3C and D). To identify the modules most relevant to disease, we analyzed the correlation between modules and clinical phenotypes. For periodontitis, the blue module showed the strongest positive correlation (r = 0.66) (Figure 3E), and for vitiligo, the blue module also exhibited the strongest positive correlation (r = 0.71) (Figure 3F). Finally, we intersected the blue modules from both diseases by drawing a Venn diagram and identified 40 overlapping genes (Figure 3G).

Enrichment Analysis of Shared Genes

Based on the aforementioned results, a total of 58 shared DEGs and 40 module overlapping genes were identified. Considering that the module genes identified by WGCNA are not all included in the DEGs and may play important roles in disease progression, we integrated the DEGs and module genes and removed duplicate genes, resulting in 93 shared genes (Supplementary Table 2). To explore the common regulatory pathways in periodontitis and vitiligo, we conducted GO and KEGG enrichment analysis on the 93 shared genes. The results indicated that these genes may be associated with response to oxidative stress, regulation of protein transport, fatty acid metabolic process, melanosome, antioxidant activity, and efferocytosis (Figure 4A). Additionally, the enrichment analysis performed using the Metascape platform also revealed that response to oxidative stress plays a common role in the pathogenesis of both periodontitis and vitiligo (Figure 4B). To further screen for shared oxidative stress-related genes in both diseases, we intersected the 93 shared genes with oxidative stress-related genes from the GeneCards database, yielding 10 candidate genes (Figure 4C). Using

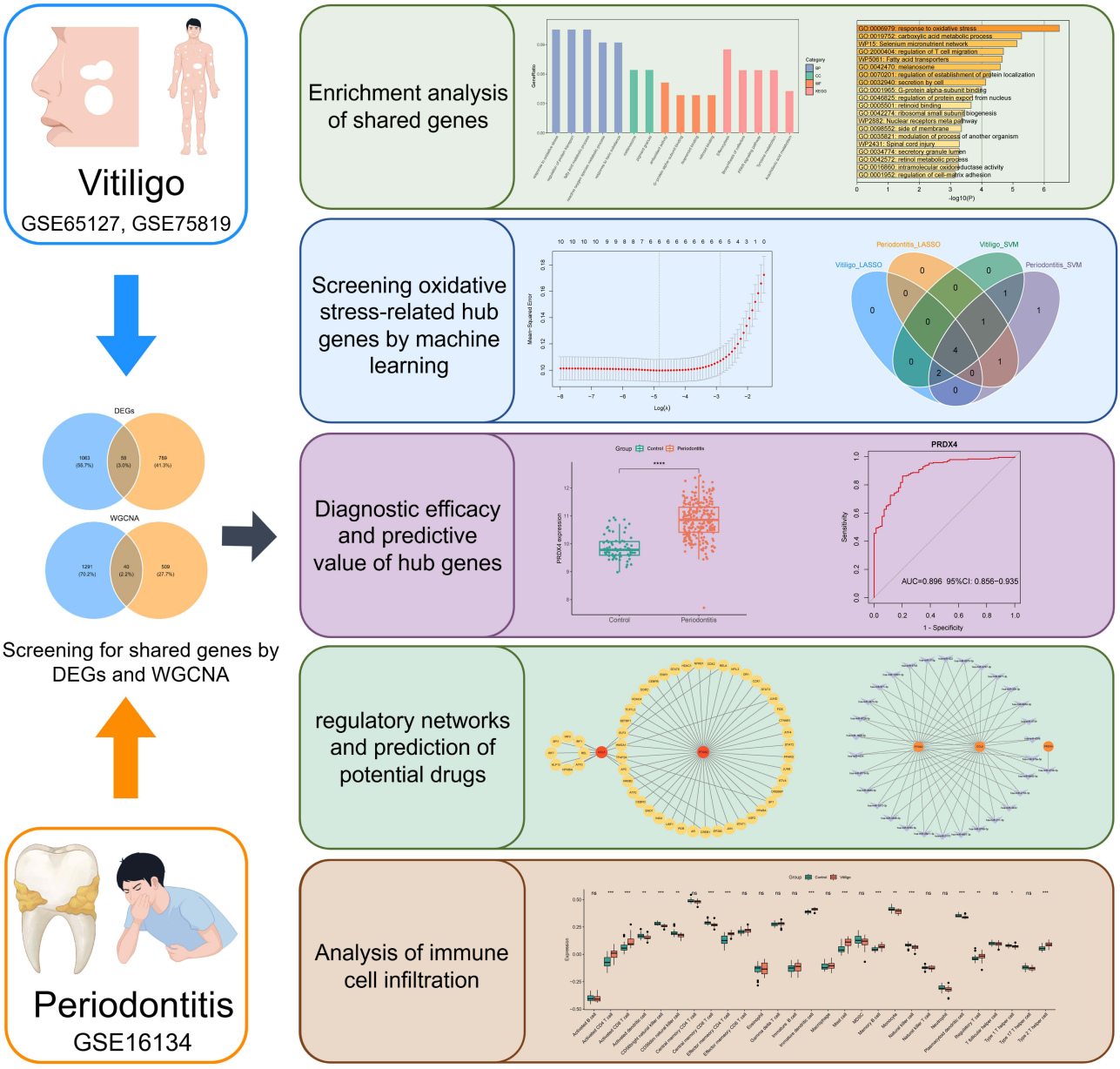

Figure 1 Research design flowchart.

the MCC algorithm in Cytoscape software, we constructed a visual network for 10 candidate genes, and finally identified TXN, SOD1, PTGS2, CD36, ARG1, CCL5, PRDX4, GLRX, UCP2, and MAPT as candidate shared biomarkers (Figure 4D).

Machine Learning for Screening Potential Shared Hub Genes

To identify shared hub genes, the 10 candidate genes were further analyzed using LASSO regression and SVM machine learning algorithms. The LASSO regression identified 6 genes in the periodontitis dataset (Figure 5A) and 6 genes in the vitiligo dataset (Figure 5B). The SVM identified 10 genes with the lowest 5-fold CV error in the periodontitis dataset (Figure 5C) and 8 genes with the lowest 5-fold CV error in the vitiligo dataset (Figure 5D). An intersection of the genes identified by both algorithms confirmed 4 final shared hub genes: PTGS2, CCL5, TXN, and PRDX4 (Figure 5E).

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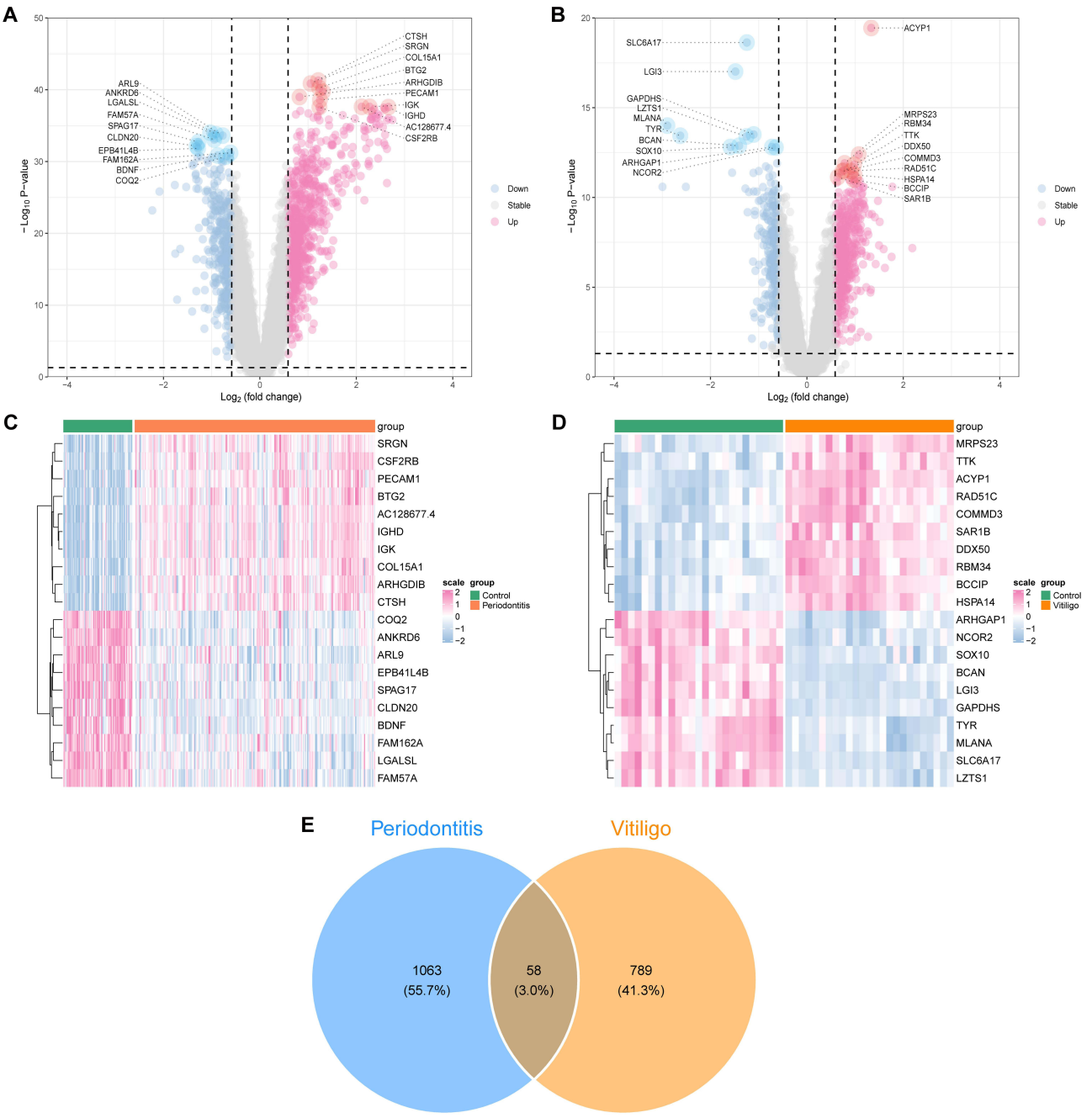

Figure 2 Identification of DEGs in periodontitis and vitiligo. (**A**) The volcano map of GSE16134, showing the distribution of DEGs in periodontitis. (**B**) The volcano map of two datasets of vitiligo, showing the distribution of DEGs in vitiligo. (**C**) The heatmap map of GSE16134, showing the top 20 distribution of DEGs in periodontitis. (**D**) The heatmap map of two datasets of vitiligo, showing the top 20 distribution of DEGs in vitiligo. (**E**) Venn diagram of overlapping DEGs.

Expression Level of Hub Genes and ROC Curve Analysis

Compared to the control, the expression of PTGS2, CCL5, and PRDX4 was upregulated in both periodontitis and vitiligo, whereas the expression of TXN was downregulated in periodontitis and upregulated in vitiligo (Figure 6A and B). Consequently, TXN was filtered out from the hub genes, resulting in three hub genes: PTGS2, CCL5, and PRDX4.

To assess the diagnostic efficacy and predictive value of the hub genes, we constructed ROC curves, using the AUC > 0.7 as the criterion for good diagnostic efficacy and predictive value. In the periodontitis dataset, CCL5 (AUC = 0.799) and PRDX4 (AUC = 0.896) demonstrated good diagnostic efficacy and predictive value (Figure 6C).

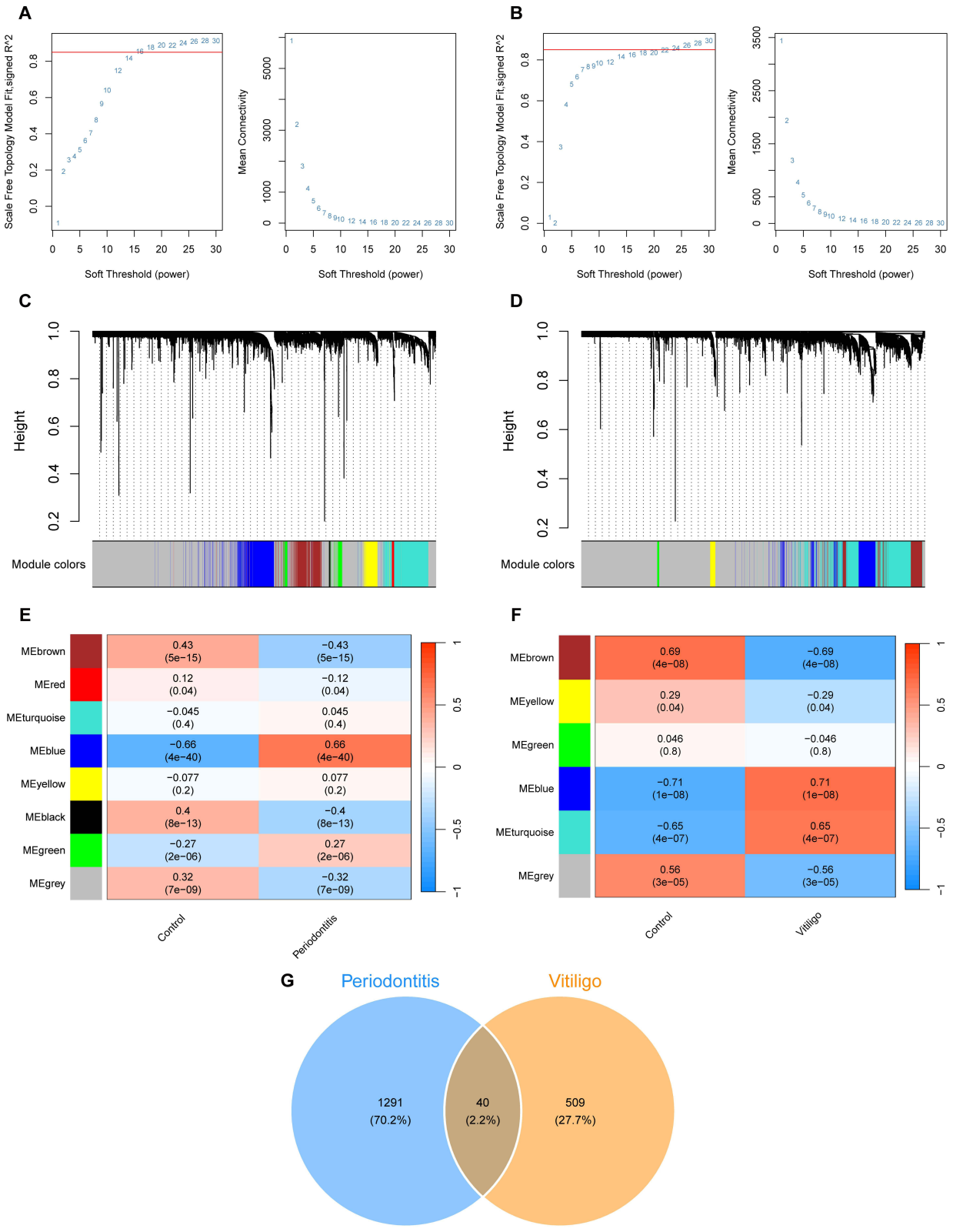

Figure 3 WGCNA analysis of periodontitis and vitiligo. (**A** and **B**) Analysis of the scale-free fit index and mean connectivity to determine the best soft-thresholding power in periodontitis and vitiligo. (**C** and **D**) Clustering dendrograms of genes in periodontitis and vitiligo. (**E** and **F**) Heatmap of the correlation analysis of module eigengenes with clinical phenotypes in periodontitis and vitiligo. Red color represents positive correlation and blue color represents negative correlation. (**G**) Venn diagram of gene module intersection between periodontitis (blue module) and vitiligo (blue module).

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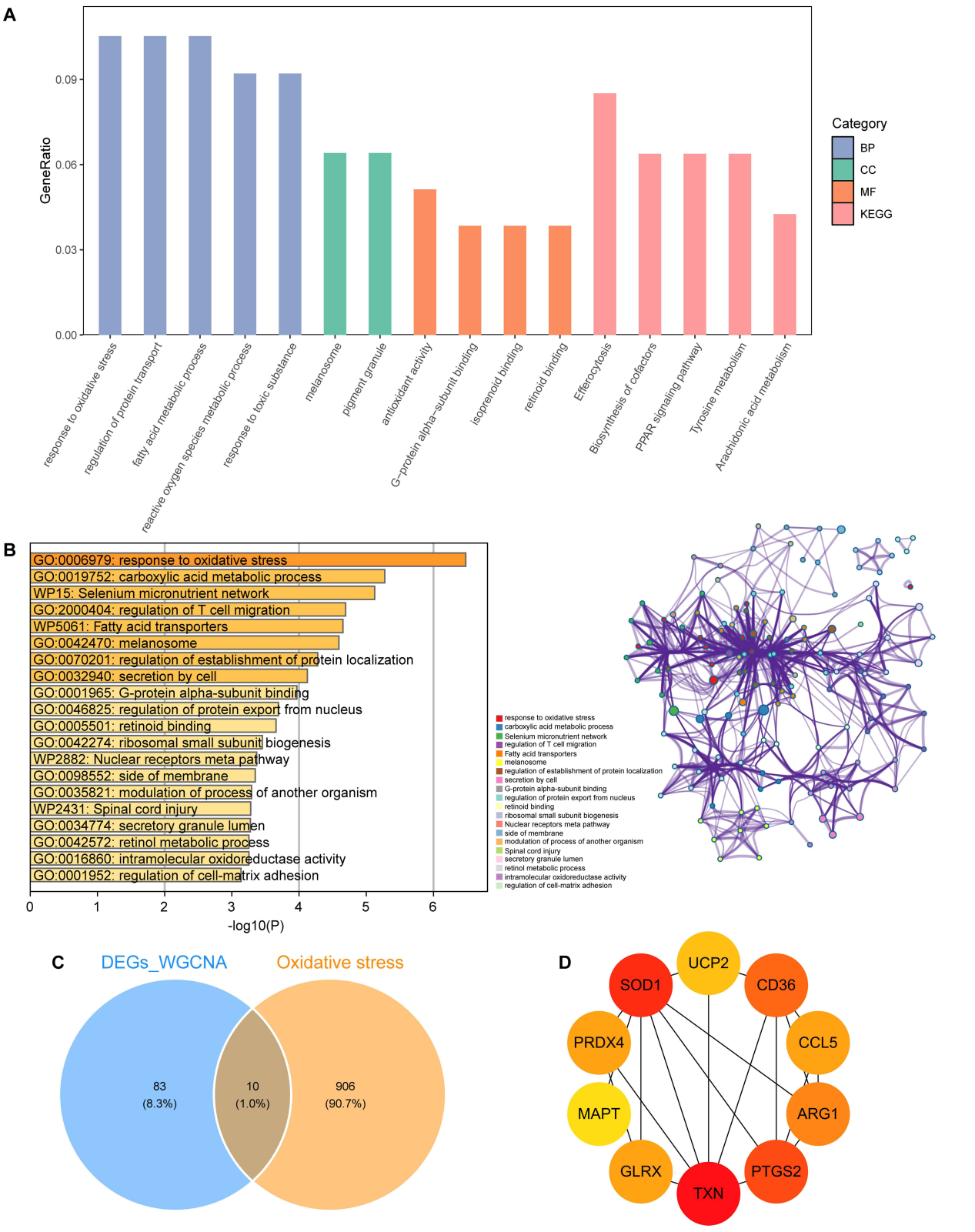

Figure 4 Functional enrichment and pathway enrichment of 93 shared genes. (**A**) GO analysis and KEGG analysis of shared genes. (**B**) Enrichment analysis of shared genes using Metascape online tool. (**C**) Venn diagram of shared genes and oxidative stress-related genes. (**D**) PPI network analysis of candidate genes using the MCC algorithm in Cytoscape.

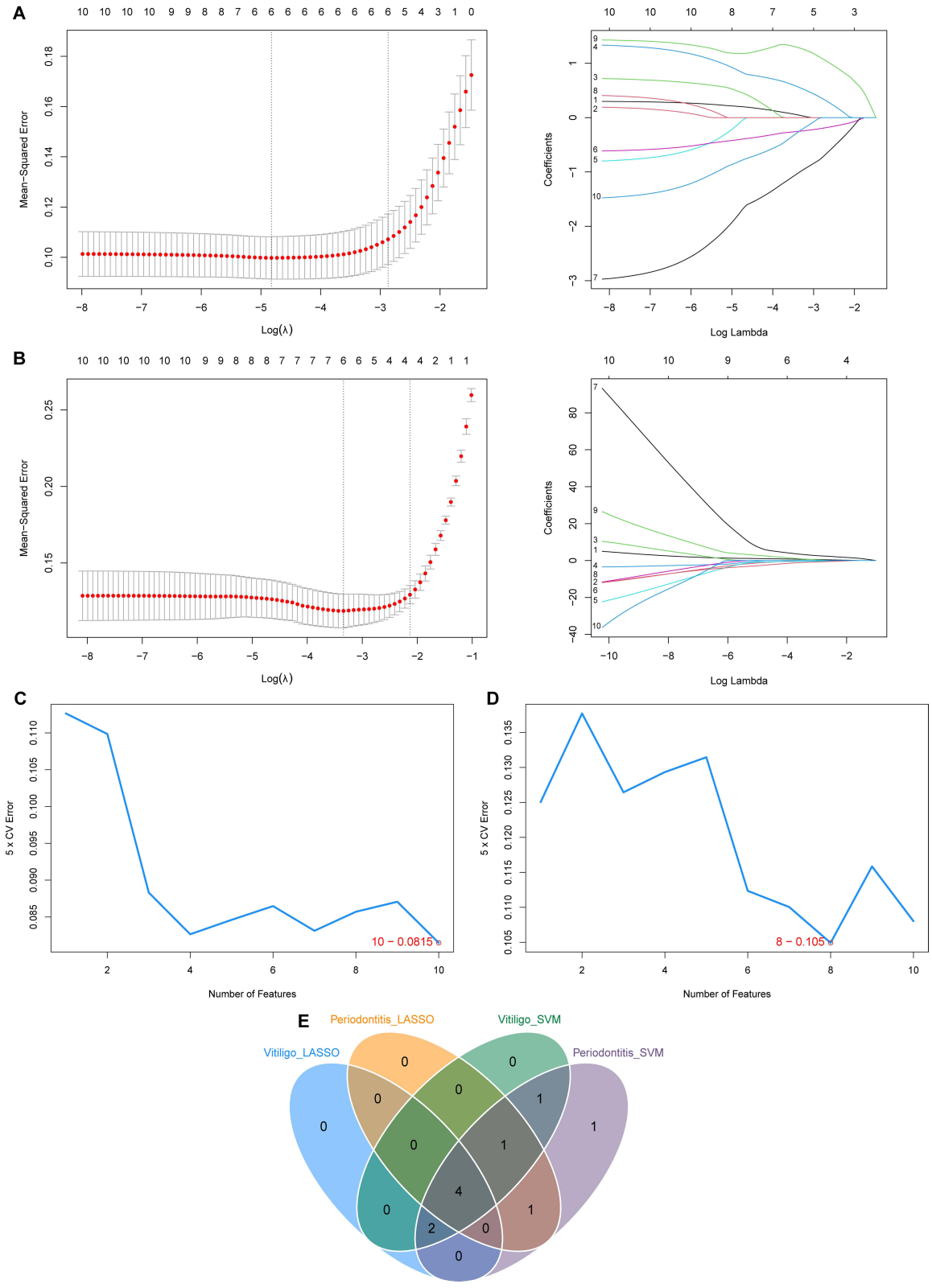

Figure 5 Identification of shared hub genes by LASSO regression and SVM. (**A** and **B**) LASSO regression analysis of periodontitis and vitiligo. (**C** and **D**) SVM analysis of periodontitis and vitiligo. (**E**) Venn diagram for the identification of hub genes through filtering with LASSO regression and SVM.

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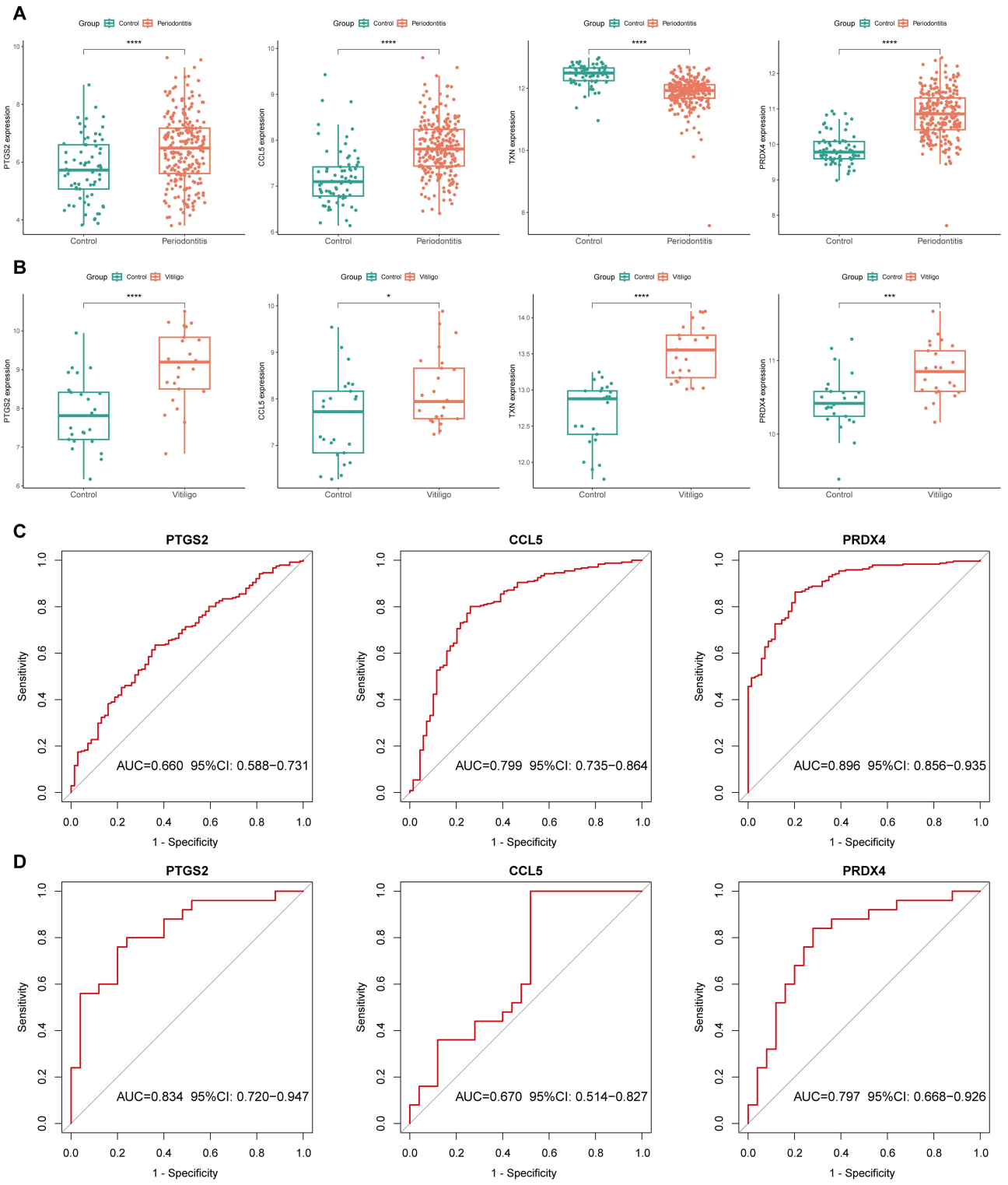

Figure 6 The expression of candidate genes and ROC curve analysis for hub genes in periodontitis and vitiligo. (**A** and **B**) Expression of four hub genes in periodontitis and vitiligo. (**C** and **D**) ROC curves for three hub genes in periodontitis and vitiligo. *p*-value: *$p< 0.05$; ***$p< 0.001$; ****$p< 0.0001$.

In the vitiligo dataset, PTGS2 (AUC = 0.834) and PRDX4 (AUC = 0.797) showed good diagnostic efficacy and predictive value (Figure 6D). These results indicate that the hub genes have robust diagnostic efficacy and predictive value for both diseases.

Construction of Regulatory Networks and Prediction of Potential Drugs

Analysis in the TRRUST database revealed that PTGS2 is associated with 43 TFs, CCL5 with 14 TFs, and the TFs common to both PTGS2 and CCL5 were NF-κB1, RELA, JUND, SP1, JUN, and CREB1 (Figure 7A). In the miRWalk database, miRNAs related to at least two hub genes were screened, resulting in a final list of 31 miRNAs (Figure 7B). The DSigDB database from the Enrichr platform identified 570 potential therapeutic agents associated with the hub genes (Supplementary Table 3), with cycloheximide, hydrogen peroxide, quercetin, Tetradioxin, and estradiol being potential drugs related to all three hub genes (Table 1).

Immune Cell Infiltration and Its Correlation with Hub Genes

Periodontitis and vitiligo are both associated with autoimmune diseases, so we conducted an analysis of immune cell infiltration and visualized the correlation between hub genes and immune cells. The results, compared to the healthy control, showed significant upregulation of activated $CD4^+$ T cells, activated $CD8^+$ T cells, immature dendritic cells, mast cells, and regulatory T cells in patients with periodontitis and vitiligo (Figure 8A and B), indicating an immune cells imbalance in both diseases.

To further investigate whether the hub genes are associated with immune cells, we conducted Spearman correlation analysis and visualized the results using heatmaps (Figure 8C and 8D). In patients with periodontitis, PTGS2 and PRDX4 were positively correlated with activated $CD4^+$ T cells (p-value < 0.05). CCL5 and PRDX4 were positively correlated with activated $CD8^+$ T cells, macrophages, and regulatory T cells (all p-value < 0.001). However, PTGS2, CCL5, and PRDX4 were negatively correlated with CD56bright natural killer cells (p-value < 0.01). PTGS2 and CCL5 were negatively correlated with CD56dim natural killer cells (p-value < 0.001) and type 17 T helper cells (p-value < 0.05).

In patients with vitiligo, similar results were observed. PTGS2, CCL5, and PRDX4 were positively correlated with both activated $CD4^+$ and $CD8^+$ T cells (all p-value < 0.001). CCL5 and PRDX4 were positively correlated with macrophages and regulatory T cells (all p-value < 0.001). However, PTGS2, CCL5, and PRDX4 were negatively correlated with CD56bright natural killer cells (p-value < 0.01) and type 17 T helper cells (p-value < 0.001). PTGS2 and PRDX4 were negatively correlated with CD56dim natural killer cells (p-value < 0.001).

This overall consistency suggests that the hub genes may modulate the immune microenvironment in both periodontitis and vitiligo.

Discussion

Previous studies have reported that vitiligo patients deficient in oral melanocytes exhibit increased gingival inflammation, which is potentially linked to oxidative stress.[13,24] Periodontitis is a chronic multifactorial inflammatory disease with a high global prevalence. For many years, there have been reports of a correlation between periodontitis and various autoimmune and chronic inflammatory skin diseases.[16,25,26] Vitiligo is an autoimmune skin disease that severely affects appearance and psychological health. Oxidative stress, which induces the destruction of melanocytes by $CD8^+$ cytotoxic T lymphocytes, is considered one of the important pathophysiological mechanisms in vitiligo.[27] Similarly, the dysbiosis of the oral microbial ecosystem in periodontitis leads to an excessive production of ROS, causing an imbalance between the body's oxidative burden and antioxidant defense capabilities, and resulting in oxidative stress between tissues. Therefore, oxidative stress may be a common pathogenic mechanism in both diseases. Identifying shared molecular markers related to oxidative stress is vital for understanding the connection between periodontitis and vitiligo and for discovering novel diagnostic and therapeutic targets.

In this study, we compiled transcriptomic data from the GEO database and used WGCNA to identify 93 shared genes between periodontitis and vitiligo. Functional enrichment analysis revealed that these genes were significantly enriched in pathways related to the response to oxidative stress, which supported our initial hypothesis. By intersecting the shared genes with oxidative stress-related genes from the GeneCards database, 10 candidate genes were selected. Subsequent screening with LASSO and SVM machine learning algorithms identified three hub genes: PTGS2, CCL5, and PRDX4. Additionally, we employed ROC curves to evaluate the diagnostic efficacy and predictive value of the hub genes. The

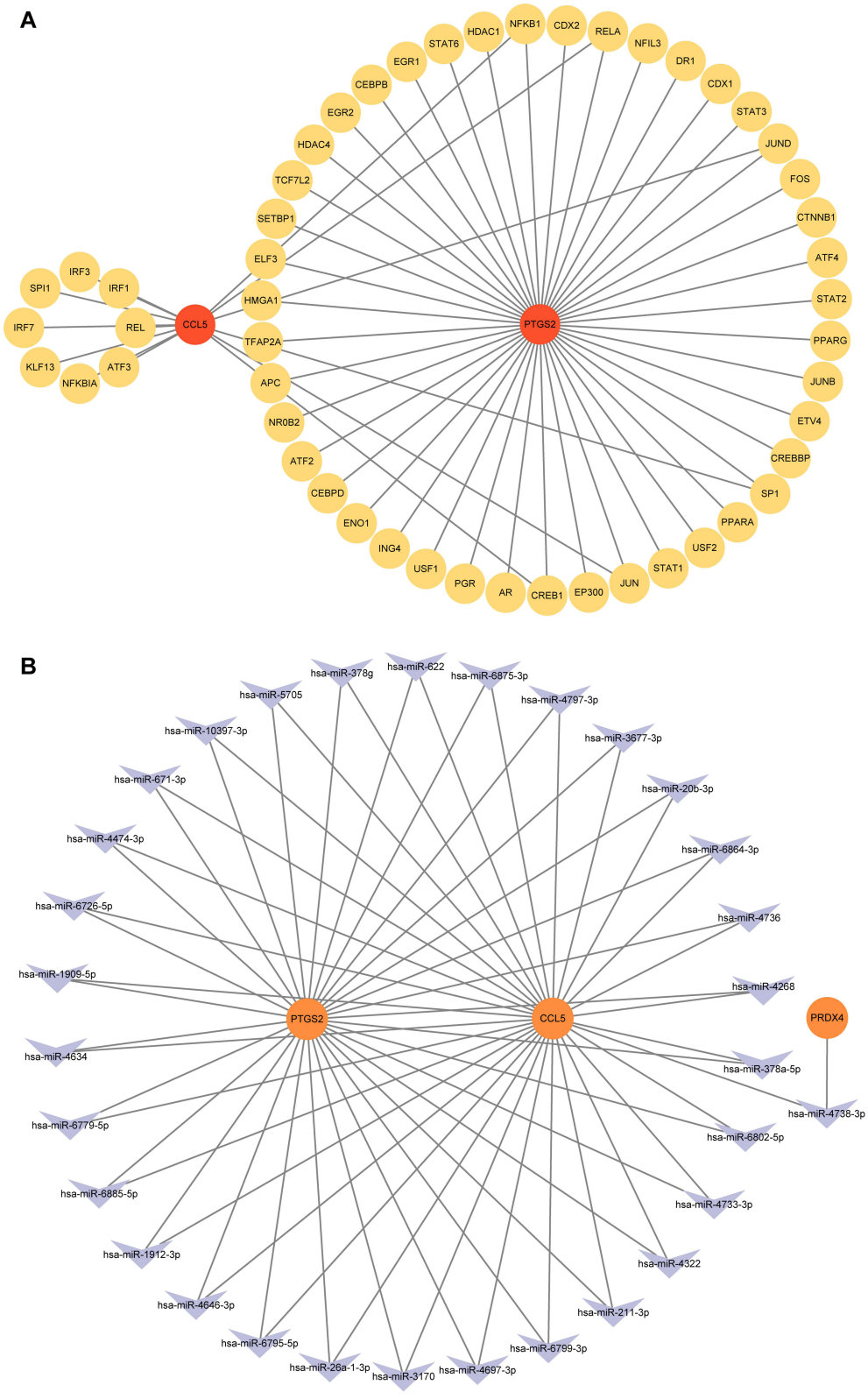

Figure 7 TFs and miRNAs regulatory networks. (**A**) TFs regulatory network. TFs were marked in yellow, and the hub genes were marked in red. (**B**) miRNAs regulatory network. miRNAs were marked in purple, and the hub genes were marked in Orange.
Abbreviations: TFs, transcription factors; miRNAs, microRNAs.

Table 1 Potential Drugs Predicted Based on Hub Gene Associations

Term	Adjusted *p*-value	Odds Ratio	Combined Score
Cycloheximide CTD 00005731	0.001	59,028	730,615.4291
Hydrogen peroxide CTD 00006118	0.016	51,981	313,891.5608
Quercetin CTD 00006679	0.016	50,526	279,822.8361
Tetradioxin CTD 00006848	0.017	48,696	243,880.3814
Estradiol CTD 00005920	0.019	46,992	215,547.2321

results demonstrated that CCL5 and PRDX4 serve as robust diagnostic and predictive markers for periodontitis, while PTGS2 and PRDX4 were similarly effective in the context of vitiligo.

PTGS2 (Prostaglandin-Endoperoxide Synthase 2), also known as cyclooxygenase 2 (COX2), is an enzyme that catalyzes the first rate-limiting step in the conversion of arachidonic acid (AA) released from phospholipase A2 into prostaglandins and thromboxane-type eicosanoids.[28] Prostaglandin E2 (PGE2), a major biologically active prostaglandin derived from AA metabolism, is primarily involved in inflammatory processes. The PTGS2/COX2-PGE2 signaling axis, which is expressed and activated during inflammation, is widely considered to be an inflammatory driver.[29] During the catalysis of arachidonic acid to prostaglandins, PTGS2 produces ROS as a byproduct. Excessive ROS directly or indirectly enhances the reactions mediated by endothelium-derived contracting factors, leading to endothelial oxidative stress.[30] Oxidative stress, in turn, can induce the expression of PTGS2, creating a vicious cycle.[31,32] Previous studies have shown that PTGS2 is upregulated in periodontitis and has a significant impact on the risk of developing the disease,[33,34] which is consistent with our findings. Compared to healthy individuals, patients with periodontitis exhibit differences in PTGS2 promoter methylation,[35] and alterations in DNA methylation could lead to a failure of inflammation resolution, an important aspect of the pathogenesis of periodontitis.[36] The laboratory research findings suggest that intercellular adhesion molecule 1 may be involved in the regulation of ferroptosis in inflammatory macrophages and human umbilical vein endothelial cells by upregulating the expression of PTGS2.[37] Notably, nicotine may participate in the occurrence and development of periodontitis by inducing PTGS2 expression, which is enhanced by oxidative stress and mediated by the extracellular signal-regulated kinase signaling pathway.[38] This suggests that PTGS2 is involved in the regulation of numerous biological processes in periodontitis and may become a potential therapeutic target for the treatment of the disease. For vitiligo, candidate gene association studies have reported a significant correlation between PTGS2 and vitiligo.[39] Multiple studies have shown that PTGS2 is upregulated in vitiligo and participates in important biological processes such as inflammatory responses and oxidative stress in melanocytes.[40–43] PTGS2 is considered one of the key target genes for vitiligo treatment, and kaempferol has shown great potential in the antioxidant therapy of vitiligo.[44] Kaempferol and quercetin have similar chemical structures. Previous studies have demonstrated that quercetin prevents alveolar bone loss in periodontitis by ameliorating oxidative stress.[45] Interestingly, our study found that quercetin may potentially serve as a therapeutic agent for vitiligo and periodontitis with PTGS2 as a target gene. This further suggests that PTGS2 may serve as a potential target gene in the antioxidant therapy.

CCL5 (C-C motif chemokine ligand 5) is a secreted small-molecule protein belonging to the CC chemokine family, expressed in blood and the tumor microenvironment.[46,47] It recruits a variety of cells, including monocytes, macrophages, mast cells, eosinophils, basophils, and dendritic cells, in response to inflammation and participates in leukocyte migration to inflamed tissues,[48] associating with the pathophysiology of autoimmune diseases.[49] CCL5 primarily acts on CCR5 (C-C motif chemokine receptor 5) to increase ROS production in blood vessels, inducing oxidative stress and contributing to the pathogenesis of hypertension.[50] Previous studies have shown that CCL5 expression is higher in patients with periodontitis than in healthy subjects,[51,52] which aligns with our findings. CCL5, as a biomarker of periodontitis, is involved in its pathological process, directly acts on osteoclasts to enhance alveolar bone destruction, and increased bacterial activity can elevate CCL5 expression.[53] However, no studies have reported whether CCL5 affects periodontitis through oxidative stress. In vitiligo, a meta-analysis of chemokines found that CCL5 expression was elevated compared to healthy controls,[54] consistent with our results. $CD8^+$ T cells in vitiligo lesional skin highly express CCL5, correctly localizing CCR5-expressing Tregs near $CD8^+$ T cells, thereby enhancing Treg function.[55] Oxidative stress may stimulate melanocytes to produce

Figure 8 Correlation of hub genes and immune cell infiltration in periodontitis and vitiligo. (**A** and **B**) Boxplots showing the pattern of immune cell infiltration in periodontitis and vitiligo. Green represents healthy controls and Orange represents periodontitis or vitiligo patients. (**C** and **D**) Heatmaps showing the correlation between hub genes and immune cells in periodontitis (**C**) and vitiligo (**D**). Orange represents positive correlation and green represents negative correlation. *p*-value: **p*< 0.05; ***p*< 0.01; ****p*< 0.001.

Abbreviation: ns, non-significant.

CXCL12 and CCL5 chemokines, leading to the recruitment of $CXCR4^+$ and $CCR3^+$ leukocytes, including antigen presenting cells and T cells, and thus contributing to the pathogenesis and progression of vitiligo.[56] This suggests that CCL5 may explain the pathophysiological mechanisms of periodontitis and vitiligo from the perspective of oxidative stress and could potentially serve as a biomarker for the concomitant presence of periodontitis and vitiligo.

PRDX4 (Peroxiredoxin 4) is the only peroxiredoxin in the endoplasmic reticulum,[57] functioning as an antioxidant and participates in redox signaling during endoplasmic reticulum stress,[58,59] serving as a protector against various inflammatory and bone-destructive diseases.[60,61] Multiple studies have shown that PRDX4 plays a crucial role in countering ROS, inhibiting both local and systemic oxidative stress.[62–64] Two previous studies have indicated that PRDX4 levels are higher in patients with periodontitis than in healthy subjects,[65,66] with a significant correlation between PRDX4 and the infiltration of activated B cells, suggesting a potential role in regulating B cells to affect periodontitis,[65] which aligns with our findings. However, no systematic investigation has been conducted to elucidate the role of PRDX4 in the pathogenesis and progression of periodontitis. Our research reveals that elevated PRDX4 exhibits good diagnostic efficacy and predictive value (AUC = 0.896) in periodontitis, and PRDX4 may influence periodontitis by regulating oxidative stress. PRDX4 also plays a significant role in skin tissue, being a key molecule in the process of skin wound healing. Overexpression of PRDX4 can ameliorate severe local and systemic oxidative stress caused by wounds and aging in skin tissue, thereby protecting wound tissue from oxidative damage.[62] Despite the lack of evidence linking PRDX4 to vitiligo, its role in mitigating oxidative stress in skin tissue suggests substantial potential as a therapeutic target gene for vitiligo treatment. Consequently, PRDX4 may emerge as an important diagnostic marker and a novel therapeutic target for the concomitant presence of periodontitis and vitiligo.

TFs play a crucial role in regulating gene expression. In this study, we used the TRRUST database to analyze hub genes and identified key TFs. Our results suggest that NF-κB1, RELA, JUND, SP1, JUN, and CREB1 may play significant roles in both periodontitis and vitiligo. Multiple bioinformatics studies have also highlighted NF-κB1, JUN, and RELA as important TFs in both diseases.[67–69] TFs, with SP1 as a prominent player, exhibit significant regulatory effects on genes with persistent dysregulation and are crucial in vitiligo.[70] This insight aids in further exploring the shared biological processes of both diseases. Additionally, we constructed a miRNAs-genes interaction network associated with hub genes, wherein miR-211 is a key regulator of cellular metabolism in vitiligo and has been implicated in chondrogenesis of periodontal ligament stem cells, potentially linking it to periodontitis.[71,72] This suggests that miR-211 may play a significant role in both diseases, which aligns with our findings. Although previous studies and our own research indicate that these TFs and miRNAs have important roles in both periodontitis and vitiligo, further experimental validation is required to confirm their accuracy and efficacy.

Considering the significant role of immune cells in the pathogenesis and progression of both periodontitis and vitiligo, we used the ssGSEA method to analyze the infiltration patterns of immune cells and revealed the correlation between hub genes and immune cell distribution. The results indicate that the immune cell profiles in both diseases show a similar distribution pattern. Compared to healthy controls, activated $CD4^+$ T cells, activated $CD8^+$ T cells, immature dendritic cells, mast cells, and regulatory T cells are significantly upregulated in both periodontitis and vitiligo, which is consistent with previous studies.[73–75] The balance between Th1 and Th2 cells plays a crucial role in the progression of periodontitis. Th1 cells enhance the cytotoxic immune response by releasing IL-12, IFN, and TNF, and are involved in the inflammatory process during the quiescent phase of periodontitis. When periodontitis is active, Th2 cells become dominant, with a significant infiltration of bone marrow-dependent lymphocytes, including B cells and plasma cells, in the periodontal tissue, while the levels of IFN and IL-12 associated with Th1 cells decrease.[76] Similarly, a balance between Tregs and Th17 cells is maintained, which shifts in favor of Th17 cells in the presence of pro-inflammatory cytokines. An excess of IL-17 produced by Th17 cells leads to the overactivation and mobilization of neutrophils and the production of chemotactic factors that promote neutrophil extravasation, thereby exacerbating tissue damage, which may be an important mechanism in periodontitis.[77] In periodontitis, the function of $CD8^+$ T cells in inhibiting inflammation, promoting bone formation, and tissue repair is suppressed, leading to the destruction of periodontal tissue.[78] Additionally, regulatory T cells may produce cytokines such as transforming growth factor β and cytotoxic T-lymphocyte antigen 4 to downregulate the inflammatory response in periodontitis.[79] In vitiligo, autoreactive cytotoxic $CD8^+$ T cells interact with melanocytes to produce IFN-γ locally, promoting disease progression.[80] Increased expression of CCL5 in vitiligo patients

may lead to eosinophil infiltration, enhancing the efficacy of $CD8^+$ T cells.[81] The impaired function of Treg cells allows uncontrolled $CD8^+$ T cell-mediated destruction of pigment cells, which is a key factor in the autoimmune pathophysiology of vitiligo.[82] Overall, immune system dysregulation is closely associated with both periodontitis and vitiligo.

In summary, this study was the first to integrate bioinformatics analysis and machine learning algorithms to identify significant oxidative stress-related shared biomarkers in periodontitis and vitiligo. We investigated the regulatory networks and potential immune cell impacts of the hub genes (PTGS2, CCL5, and PRDX4), and assessed their diagnostic efficacy and predictive value. Furthermore, based on the hub genes, potential therapeutic drugs were predicted.

This study has several limitations. First, the analysis relied solely on publicly available transcriptomic datasets. Differences in sequencing platforms, demographic variability, and limited sample size may introduce potential biases. Second, we did not perform experimental validation in cellular or animal models to further confirm the reliability of the bioinformatic results. Therefore, before these three shared biomarkers can be applied clinically, rigorous experimental validation is essential. Finally, for future studies, we aim to collect patient samples to validate the expression of the hub genes and elucidate their functional role in the shared oxidative stress pathways in both diseases.

Conclusion

This study identified oxidative stress as a potential common pathogenic mechanism in periodontitis and vitiligo. We identified PTGS2, CCL5, and PRDX4 as key shared biomarkers and demonstrated that both diseases exhibit similar immune infiltration patterns. Consequently, targeting the immune response and oxidative stress represents a promising therapeutic strategy for both conditions. Future experimental and clinical studies are essential to validate these biomarkers and translate the findings into diagnostic and therapeutic applications.

Data Sharing Statement

The datasets presented in this study can be found in public databases or the supplementary materials. Further inquiries can be directed to the corresponding authors.

Ethical Statement

In accordance with Article 32 of the Measures for the Ethical Review of Life Sciences and Medical Research Involving Humans (National Science and Technology Ethics Committee, China), this study was a secondary analysis of publicly available data, granted an exemption from ethical review by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (Ethics Number: ES-MS-2025-005).

Acknowledgments

The authors extend sincere gratitude to all the affiliated researchers for their contributions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Guangdong Medical Science and Technology Research Fund Project (A2020294) and Guangzhou City University (Institute) Joint Funding for Basic and Applied Basic Research (202201020405).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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