Regenerative Medicine and Dentistry
https://www.sciltp.com/journals/rmd

Article

Unraveling the Underlying Comorbidity Mechanisms of Atopic Dermatitis and Periodontitis via Bioinformatics

Kaiye Lin [1], Lv Xie [2,3], Guangqi Gao [2,3], Yingye Zhang [2,3], Na Li [2,3], Chunxiao Lv [2,3,*] and Zetao Chen [2,3,*]

[1] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, Guy's Hospital, London SE1 9RT, UK
[2] Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, and Guangdong Provincial Key Laboratory of Stomatology, Guangzhou 510055, China
[3] Guangdong Research Center for Dental and Cranial Rehabilitation and Material Engineering, Guangzhou 510055, China
* Correspondence: lvchx@mail.sysu.edu.cn (C.L.); chenzet3@mail.sysu.edu.cn (Z.C.)

How To Cite: Lin, K.; Xie, L.; Gao, G.; et al. Unraveling the Underlying Comorbidity Mechanisms of Atopic Dermatitis and Periodontitis via Bioinformatics. *Regenerative Medicine and Dentistry* **2025**, *2*(4), 17. https://doi.org/10.53941/rmd.2025.100017

Received: 14 September 2025
Revised: 10 October 2025
Accepted: 16 October 2025
Published: 27 October 2025

Abstract: Purpose: Atopic dermatitis (AD) and periodontitis (PD) exhibit overlapping immune and adhesion processes (e.g., Th2-skewing in AD and Th1/Th17 responses with Th2 components in PD). We aimed to identify shared transcriptomic signatures and prioritise candidate genes, miRNAs, and transcription factors linking AD and PD using integrative bioinformatics to generate hypotheses for subsequent experimental and clinical validation. **Methods:** Expression profiles from AD (GSE120721, GSE182740) and PD (GSE16134, GSE23586) datasets were analyzed. Differentially expressed genes (DEGs) shared between both conditions were identified and validated. Analyses included GO and KEGG enrichment, PPI network construction, and identification of hub genes, miRNA interactions, and transcription factors. **Results:** 124 DEGs were identified, with 13 hub genes enriched in immune response and cell adhesion pathways. Machine learning refined these to 4 key genes (CD69, MMP9, PXDN, VCAM1). ROC analysis validated these genes' diagnostic efficacy (AUC > 0.7). Networks of key genes with miRNA and transcription factors (NFKB1, RELA, IRF1, EP300, JUN, IKBKB). Key miRNAs included hsa-miR-9-5p, hsa-miR-21-5p, hsa-miR-143-3p, and hsa-miR-155-5p. We also demonstrated the diagnostic potential of these genes (AUC > 0.7) across both conditions. **Conclusions:** The hub genes, key miRNAs, and transcription factors identified in this study may serve as biomarkers and candidate therapeutic targets for AD and PD comorbidity. These findings are hypothesis-generating and warrant experimental validation and prospective clinical studies to assess disease relevance and potential clinical utility.

Keywords: atopic dermatitis; bioinformatics; differentially expressed genes (DEGs); machine learning; periodontitis

1. Introduction

Atopic dermatitis (AD) is a persistent and stubborn skin condition characterized by recurring symptoms such as itching, redness of the skin, dryness, thickening, and swelling [1–3]. Globally, AD impacts approximately 15–30% of children and 2–10% of adults [4,5]. At the same time, a study revealed that the quality of life of adult AD patients is significantly reduced, especially for those with moderate to severe AD. They reported lower overall health assessments, decreased satisfaction with life, lower mental and physical health scores, and higher Dermatology Life Quality Index (DLQI) scores [6]. Despite progress in AD research in recent years, current treatment methods still do not fully meet the needs of patients, especially those with poor treatment outcomes.

The development of AD is similarly complex, encompassing both classical immune cells and cytokines. AD's development is significantly influenced by the imbalance within the adaptive immune system, orchestrated by diverse T cell subsets. The discovery of novel CD4+ T cell subsets, such as Th9, Th17, and Th22 cells, sheds light on the complex immunological backdrop of AD. This new understanding underscores the necessity of targeting specific CD4+ T cell-derived cytokines for immunomodulation, particularly given the underlying skin barrier defects [7]. The heterogeneity of immune responses in AD is marked by the activation of Th2, Th22, Th17/IL-23, and Th1 cytokine pathways. This immunological diversity is pronounced among different AD subtypes, including intrinsic (a subtype without skin barrier impairment), pediatric, and Asian forms of AD [8]. But based on these studies, no suitable therapeutic target for AD has yet been found.

Recent observations have uncovered an interesting trend. Epidemiological studies have identified an increased likelihood of individuals with AD also experiencing periodontitis (PD). A study conducted in Saudi Arabia found a significant correlation between poor oral health and the prevalence of AD among adults, with a focus on oral health conditions commonly associated with AD [9]. While a study involving Swedish adults explored associations between AD and oral health conditions, it did not find a significant positive relationship between AD and PD after accounting for confounding factors [10]. This suggests that the probability of encountering AD is elevated in individuals with PD compared to those without PD.

The pathogenesis of PD is relatively well-understood, for example, through theories such as the Pathways of Tissue Destruction via MMPs and the interactions within the RANK/RANKL/OPG system [11]. Interestingly, scholars have discovered that AD and PD are closely related in terms of their immune responses. Recent research emphasizes the complex interplay between AD and PD through the Th2 immune response, despite their differing presentations and clinical outcomes. In AD, the pathology is primarily supported by a Th2-dominant immune response, leading to allergic inflammation and compromised skin barrier function. Conversely, PD is mainly driven by a Th1/Th17 response to bacterial invasion, but Th2 responses also play a significant role in shaping the disease's immune landscape, affecting its progression and severity. The research suggests the possibility of more common targets between AD and PD. This points to the potential for uncovering more in-depth codes that regulate the immune response, which remain to be deciphered. It highlights the importance of further investigating their shared immune pathways to find new therapeutic strategies for both conditions [12,13]. Deciphering these interconnections is crucial for the development of targeted therapeutic strategies aimed at modulating these immune responses, thus providing effective treatment or management options for these diseases. This suggests a potential overlap between AD and PD, making it imperative to explore whether there is a common mechanism or target between them that could guide changes in current treatment strategies.

The association between PD and various systemic diseases, including cardiovascular disease [14,15], cancer [16], rheumatoid arthritis [17], and diabetes [18], has been well established. In the case of diabetes, a systematic review evaluated the impact of periodontal treatment on glycemic control in patients with the condition. Based on moderate-certainty evidence from 35 studies, it was observed that an average absolute reduction of 0.43% (4.7 mmol/mol) in HbA1c occurred 3 to 4 months after periodontal treatment. This finding supports the clinically significant effect of periodontal treatment in improving glycemic control in patients with diabetes [19]. If we can find a common mechanism or target between PD and AD, in some sense, it may be possible to treat AD by treating PD.

As gene sequencing technology has advanced, research indicates abnormal gene expression in the skin of AD patients, yet the significance of each gene remains uncertain. Consequently, identifying sensitive and specific biomarkers that influence AD progression is crucial. This will help clarify the underlying molecular mechanisms, provide a predictive prognosis, and support the development of new targeted treatments. Emerging evidence suggests that AD and PD share immune–adhesion programs. We hypothesize a cross-disease axis in which Th2-skewed barrier dysfunction in AD elevates systemic cytokines and endothelial adhesion (e.g., VCAM1), while periodontal dysbiosis with Th1/Th17 responses promotes mediators that may sustain AD flares. Therefore, we focus on shared transcriptomic signatures (e.g., CD69, MMP9, PXDN, VCAM1, and NF-κB–related pathways) as hypotheses for further investigation, rather than asserting causality. Our analyses are aimed at prioritizing molecules and pathways along this axis as hypotheses for future testing.

2. Materials and Methods

2.1. Data Source and Preparation

Data were sourced from the GEO database [20] using "Atopic Dermatitis" and "Periodontitis" as search terms. Inclusion criteria included human samples with both case and control profiles from specific tissues—skin for AD and gum for PD, using consistent sequencing platforms (GPL570) without prior clinical interventions.

For the two PD datasets and two AD datasets, batch correction was carried out using the "SVA" package in R (version 4.3.1). This process combined the two PD datasets into a cohort with 100 control samples and 343 PD samples, and the two AD datasets into a cohort with 28 control samples and 98 AD samples. Principal component analysis (PCA) of the expression values was performed before and after batch correction using the "vegan" package, and the results were visualized with the "ggplot2" package. Probe IDs were converted to gene symbols based on annotation files. When multiple probes corresponded to a single gene, the gene expression value was averaged across these probes, and probes that did not correspond to any gene symbols were excluded.

Identifying common differentially expressed genes DEGs were identified using the "limma" R package, focusing on genes with an absolute $|\log FC| \geq 0.5$ and an adjusted p-value < 0.05. The threshold for the log fold change was chosen to capture biologically significant changes in gene expression, while the p-value adjustment was performed using the Benjamini-Hochberg method to control for false discovery rates. Results were visualized with "ggplot" and "ggvenn". The analysis was conducted on R. To preserve concordant regulation, we first identified the overlap of genes that were up-regulated in both AD and PD, and separately the overlap of genes that were down-regulated in both diseases. This prevents inclusion of genes changed in opposite directions across diseases (for example, up in AD but down in PD, or vice versa), which would dilute enrichment signals and are not consistent with a shared comorbidity axis. For downstream enrichment and network analyses, we used the combined set of concordantly regulated genes ($n = 124$) for statistical stability

2.2. Rationale and Boundaries of Cross-Tissue Comparisons

Our analysis integrates transcriptomic datasets from distinct tissues—skin in AD and gingival/periodontal tissues in PD. Since directly pooling across tissues may confound tissue-specific expression with disease signals, we analyzed datasets within each disease separately and then compared convergent patterns in differentially expressed genes, protein–protein interactions, and pathway/TF/miRNA enrichment. We focused our interpretation on shared immune and adhesion pathways rather than absolute gene-level concordance across tissues. Thus, all cross-tissue findings are considered hypothesis-generating. Potential limitations include residual batch effects, differences in sample processing, and clinical heterogeneity (e.g., age, sex, smoking, and comorbidities), underscoring the need for prospective validation.

2.3. Analysis of Enrichment for Common DEGs

Functional enrichment was conducted via the "clusterProfiler" R package, analyzing DEGs by GO and KEGG databases. The GO analysis contains three terms: biological process, cellular component, and molecular function. The R Package "ggplot2" was used for visualization.

2.4. Construction of PPI Networks and Detection of Hub Genes, and Enrichment Analysis of Hub Genes

Protein-protein interactions were analyzed using the String database [21] with a significance threshold of 0.4. Hub genes were identified using Cytohubba algorithms and MCODE within Cytoscape [22,23]. Results were visualized with "ggvenn". Functional enrichment was conducted via the "clusterProfiler" R package, analyzing DEGs against the GO and KEGG databases.

2.5. Feature Selection Using LASSO and SVM-RFE Methods and Identification of Key Genes for Both Diseases

Feature genes were identified using LASSO and SVM-RFE via the "glmnet" and "e1071" packages, respectively, with a focus on optimizing feature selection and employing 5-fold cross-validation. Key genes of two diseases were identified by finding the overlapping hub genes and feature genes. The results were visualized using "ggvenn".

2.6. Determining the Diagnostic Efficacy of Key Genes

The diagnostic capabilities of key genes were assessed using the 'pROC' package in R, focusing on their predictive power expressed through Area Under the Curve (AUC) metrics for both AD and PD contexts. We validated the results using external datasets; for the external datasets, we selected GSE10334 for PD and GSE130588 for AD.

2.7. Investigation of Shared miRNAs in Two Diseases and Construction of the Shared miRNAs-mRNA Network

Shared miRNAs associated with both AD and PD were identified using the Human MicroRNA Disease Database (HMDD) [24–26]. The network of interactions between miRNAs and mRNAs, specifically those shared between AD and PD, was explored using experimentally validated data from the miRTarBase [27]. Functional analysis of miRNAs

was carried out using TAM 2.0 (http://www.lirmed.com/tam2 (accessed on 12 March 2024)) [28]. This analysis aimed to identify potential regulatory mechanisms that might influence both conditions.

2.8. Construction of the TF-Key Genes Network

The TRRUST database (Transcriptional Regulatory Relationships Unraveled by Sentence-based Text mining; https://www.grnpedia.org/trrust/ (accessed on 12 March 2024)) [29] was utilized to predict transcriptional regulatory networks.

3. Results

3.1. Data Source and Preparation

During the present study, we structured a research flowchart (Figure 1). After applying the predefined selection criteria, several Gene Expression Omnibus (GEO) datasets were identified as relevant for this study: GSE16134, GSE23586, GSE120721, and GSE182740. After merging the two datasets for PD and AD, we performed principal component analysis (PCA) on them, followed by batch correction, resulting in the outcomes (Figure 2A–D).

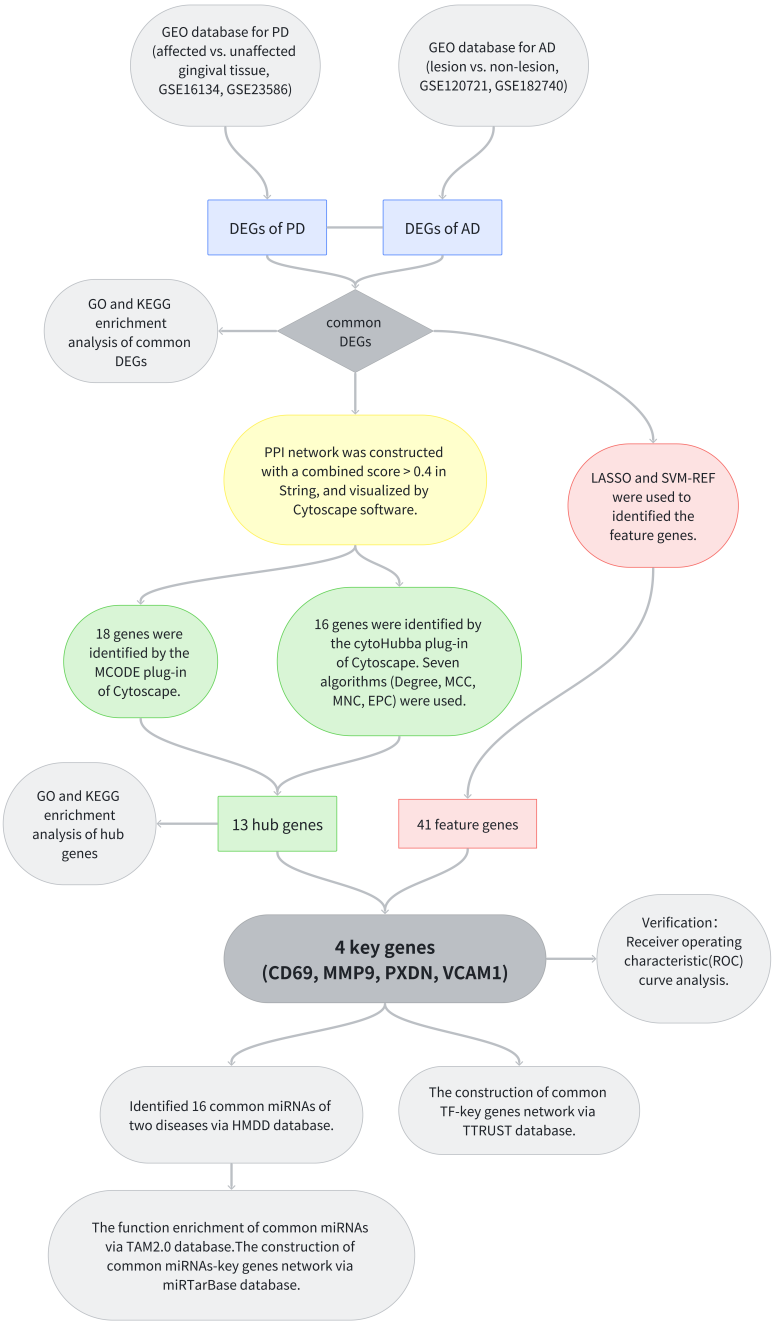

Figure 1. Flowchart of the study.

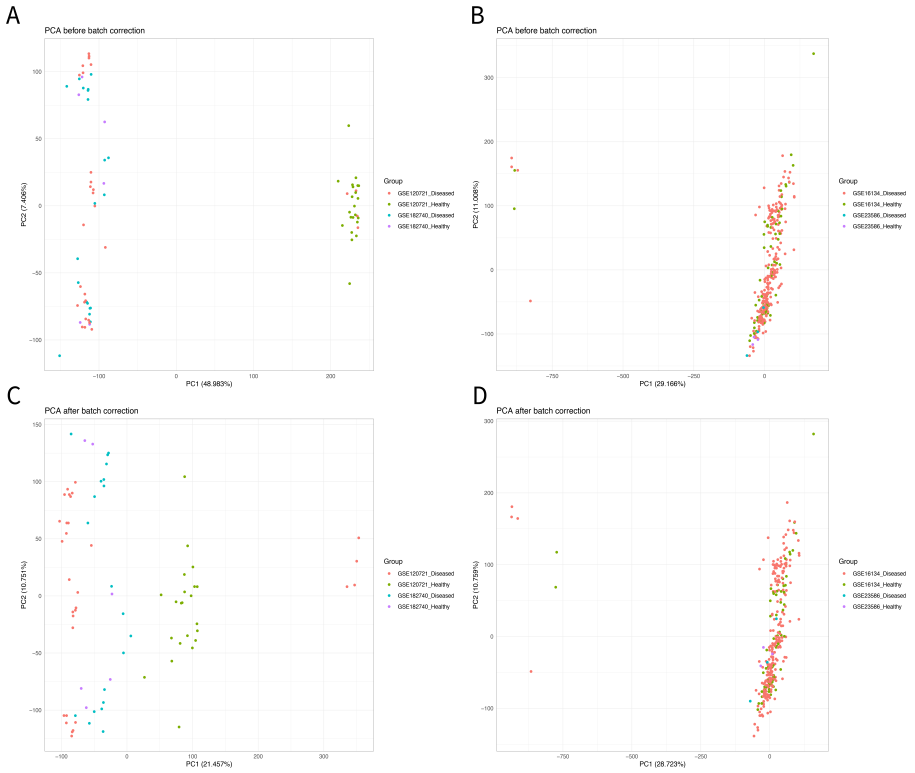

Figure 2. PCA analysis of gene expression data before and after batch correction. (**A**): PCA before batch correction (Dataset 1: Merged PD Data) (**B**): PCA before batch correction (Dataset 2: Merged AD Data) (**C**): PCA after batch correction (Dataset 1: Merged PD Data) (**D**): PCA after batch correction (Dataset 2: Merged AD Data).

3.2. Identifying Common Differentially Expressed Genes

Using the threshold p-value < 0.05 and logFC > 0.5, we identified 560 upregulated genes and 620 downregulated genes in the PD dataset, totaling 1180 differentially expressed genes (Figure 3A). In the AD dataset, we found 1983 upregulated genes and 123 downregulated genes, totaling 2106 differentially expressed genes (Figure 3B). By intersecting the upregulated genes in PD and AD, we obtained 116 common upregulated genes (Figure 3C). Similarly, by intersecting the downregulated genes in PD and AD, we identified 8 common downregulated genes (Figure 3D). We refer to the combined concordantly regulated set (n = 124) as the shared signature for downstream enrichment and network analyses.

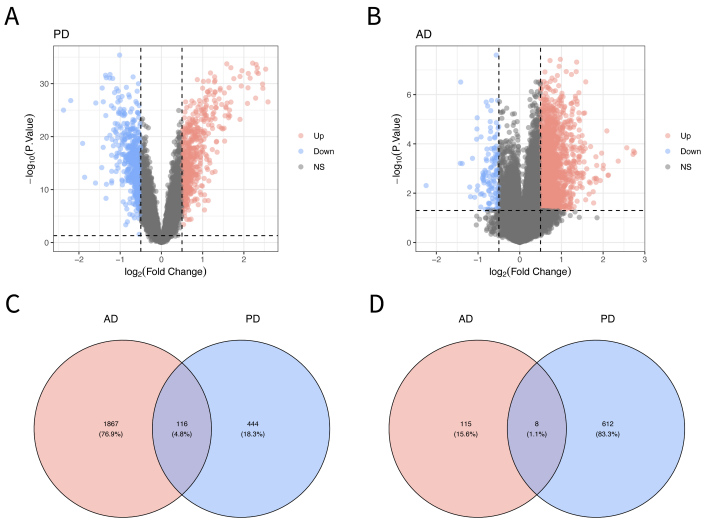

Figure 3. Identification of differentially expressed genes in PD and AD datasets. (**A**): Volcano plot of differentially expressed genes (DEGs) in PD datasets. (**B**): Volcano plot of differentially expressed genes (DEGs) in AD datasets. (**C**): Venn diagram showing the intersection of upregulated genes in PD and AD. (**D**): Venn diagram showing the intersection of downregulated genes in PD and AD.

3.3. Analysis of Enrichment for Common DEGs

GO analysis indicated significant involvement in biological processes such as leukocyte migration, T cell activation, and response to bacterial origin molecules. Cellular component analysis highlighted significant enrichment in the external side of the plasma membrane, the secretory granule membrane, and the extracellular matrix. Molecular function analysis revealed significant enrichment in activities such as peptidase activity, enzyme activator activity, and carbohydrate binding (Figure 4A). The KEGG pathway enrichment analysis showed significant pathways including cell adhesion molecules, lipid and atherosclerosis, cytokine-cytokine receptor interaction, Staphylococcus aureus infection, and viral protein interaction with cytokine and cytokine receptor. Other notable pathways include neutrophil extracellular trap formation, TNF signaling pathway, and leukocyte transendothelial migration (Figure 4B).

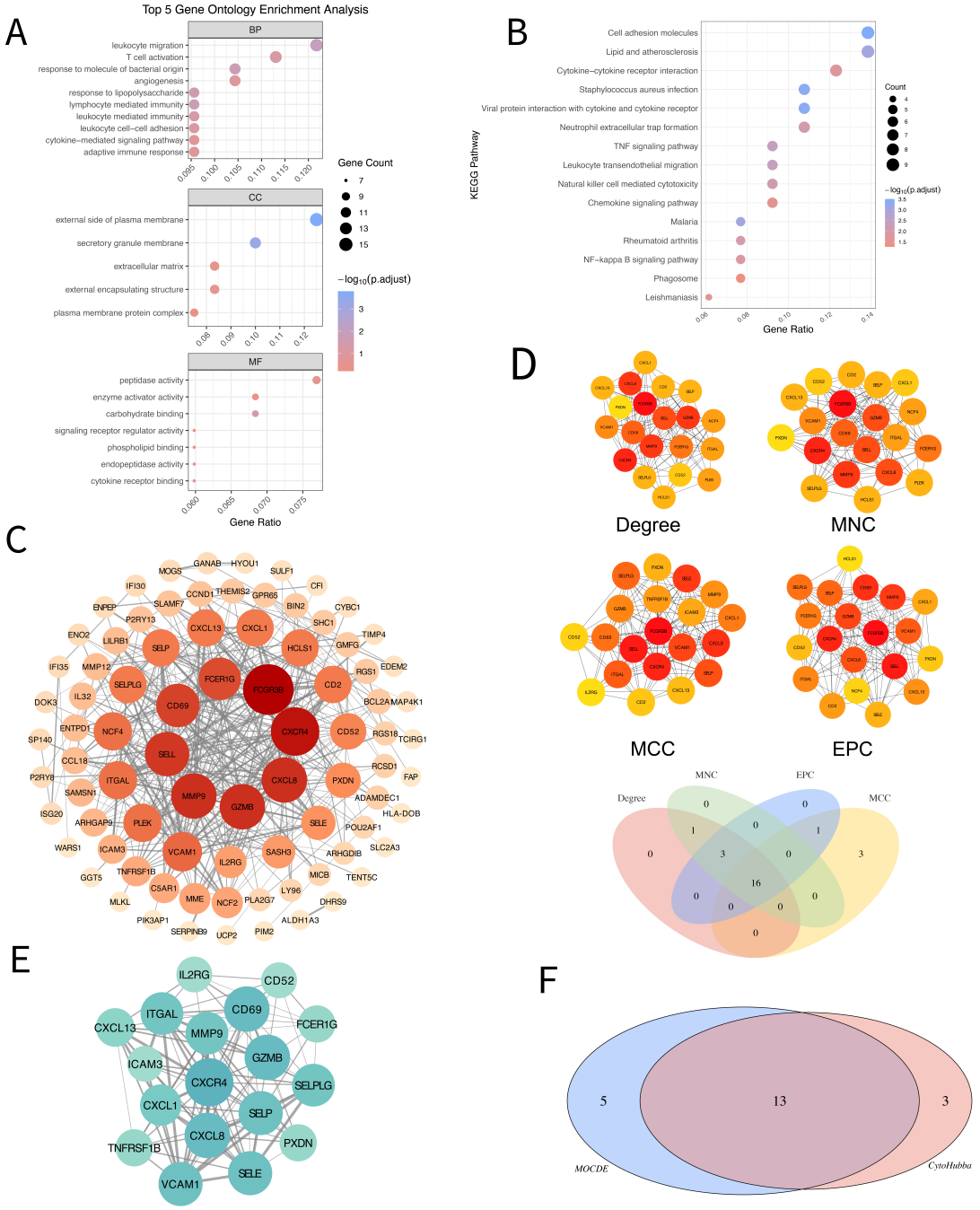

Figure 4. Analysis of enrichment for common DEGs and Construction of PPI networks, and detection of hub genes. (**A**): GO enrichment analysis of common DEGs. (**B**): KEGG pathway enrichment analysis of common DEGs. (**C**): Construction of PPI networks among common DEGs. (**D**): Detection of hub genes using CytoHubba algorithms. (**E**): Identification of genes using the MCODE plugin. (**F**): Intersection of genes identified by CytoHubba and MCODE.

3.4. Construction of PPI Networks and Detection of Hub Genes

Utilizing Cytoscape, we constructed PPI networks highlighting 84 nodes and 370 edges among the DEGs (Figure 4C). Subsequently, the identification and selection of hub genes were facilitated by employing four widely recognized algorithms provided by CytoHubba: Degree, MNC, MCC, and EPC. We selected the top 20 genes from each algorithm and took the intersection, resulting in 16 genes (Figure 4D). Concurrently, we used the MCODE plugin to identify 18 genes (Figure 4E). Finally, the intersection of genes identified by CytoHubba and MCODE resulted in 13 hub genes: ITGAL, CD69, GZMB, CXCL13, PXDN, CXCR4, VCAM1, MMP9, CXCL1, SELP, CXCL8, SELPLG, and CD52 (Figure 4F).

3.5. Construction of LASSO and SVM-RFE Feature Selection Process and Identifying Key Genes of Two Diseases

Using LASSO regression, we identified 61 potential feature candidate genes and displayed the results in a Deviance plot from Lasso cross-validation (Figure 5A). The SVM-RFE algorithm further refined the selection to 51 feature candidate genes (Figure 5B), with validation demonstrated through an accuracy curve from 5-fold cross-validation (Figure 5C). The intersection of these datasets yielded 41 feature genes, which were cross-referenced with hub genes identified in the Protein-Protein Interaction (PPI) network to pinpoint 4 definitive key genes (Figure 5D).

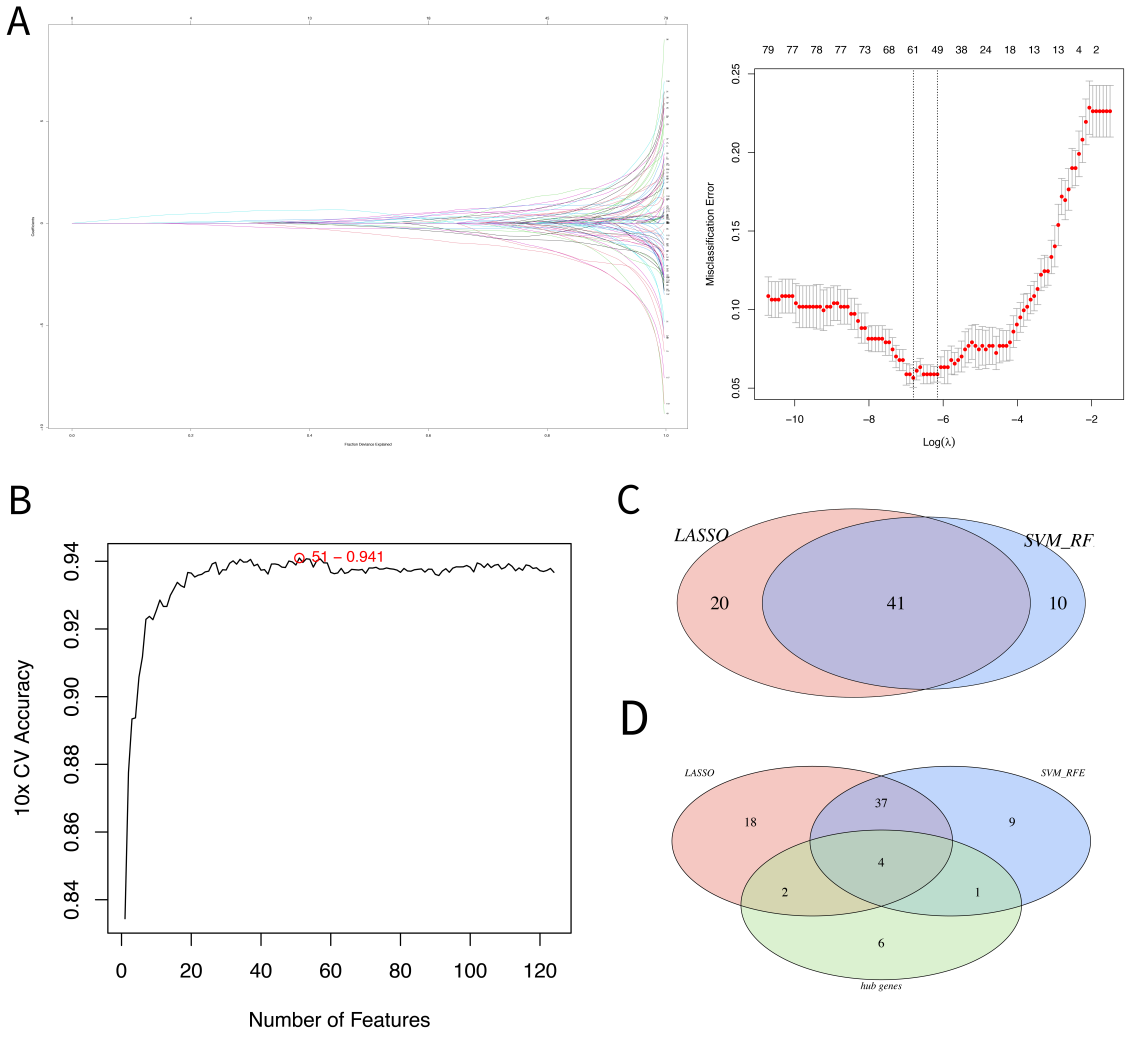

Figure 5. Construction of LASSO and SVM-RFE feature selection process and identifying key genes of two diseases (**A**): LASSO regression feature selection. (**B**): SVM-RFE feature selection. (**C**): Venn diagram showing the intersection of feature genes identified by LASSO and SVM-RFE. (**D**): Venn diagram showing the intersection of feature genes and hub genes from the PPI network.

3.6. Determining the Diagnostic Efficacy of Central Key Genes

ROC analysis was conducted to measure the diagnostic value of hub genes, represented by the Area Under the Curve (AUC). Individual ROC curves were calculated for each key gene (CD69, MMP9, PXDN, and VCAM1)

to assess their diagnostic efficacy. The AUC values for each gene were individually calculated to evaluate their potential for diagnostic application in both AD and PD conditions. In the PD cohort, the AUC values for the hub genes were as follows: CD69 had an AUC of 0.803, MMP9 had an AUC of 0.810, PXDN had the highest AUC at 0.815, and VCAM1 had an AUC of 0.717 (Figure 6A). In the AD cohort, the AUC values for the hub genes were as follows: CD69 had the highest AUC at 0.916, MMP9 had an AUC of 0.819, PXDN had an AUC of 0.63, and VCAM1 had an AUC of 0.698 (Figure 6B). These results highlight the robust diagnostic performance of these hub genes in both PD and AD cohorts, particularly CD69 and PXDN, which showed high AUC values in both cohorts.

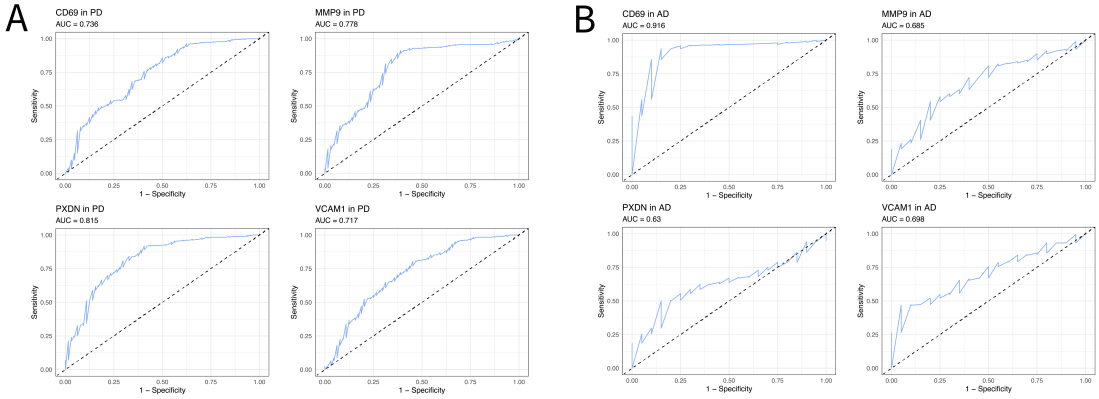

Figure 6. Determining the diagnostic efficacy of central key genes. (**A**): ROC analysis for hub genes in the PD cohort. CD69: AUC = 0.803; MMP9: AUC = 0.810; PXDN: AUC = 0.815 (highest); VCAM1: AUC = 0.717. (**B**): ROC analysis for hub genes in the AD cohort. CD69: AUC = 0.916 (highest); MMP9: AUC = 0.819; PXDN: AUC = 0.63; VCAM1: AUC = 0.698.

3.7. Investigation of Shared miRNAs in Two Diseases and Construction of the Shared miRNAs-mRNA Network

Utilizing the Human microRNA Disease Database (HMDD), we identified 42 miRNAs associated with AD and 98 miRNAs linked to PD. An intersection analysis revealed 16 miRNAs common to both AD and PD, as illustrated in the Venn diagram (Figure 7A). These miRNAs play critical roles in regulating a variety of biological processes, including Stem Cell Regulation, Cell Cycle, Inflammation, Aging, Hormone-mediated Signaling Pathways, Cell Death, Cell Proliferation, Immune Response, Innate Immunity, and Cell Differentiation. Through miRTarBase, we identified 4 key miRNAs targeting the hub genes. The identified miRNAs are hsa-miR-9-5p, hsa-miR-21-5p, hsa-miR-143-3p, and hsa-miR-155-5p. A network of miRNAs-mRNAs was established, illustrating the connections between these 4 miRNAs and 3 hub genes: PXDN, MMP9, and VCAM1. This network highlights the regulatory interactions between the miRNAs and the key hub genes, showing the potential post-transcriptional regulation involved (Figure 7B).

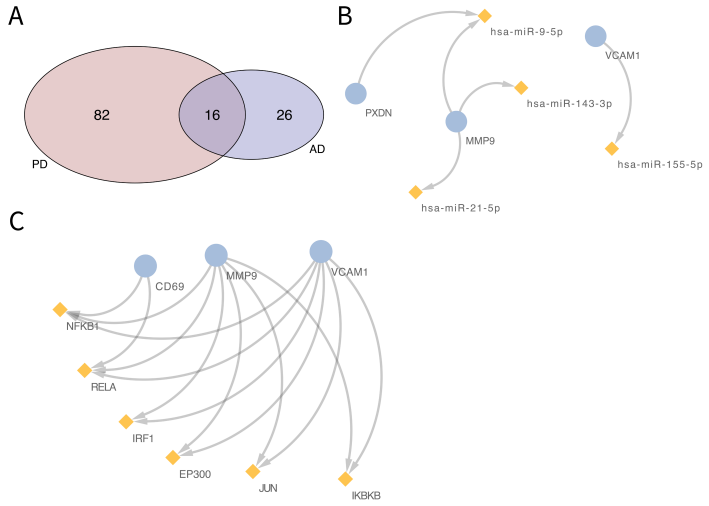

Figure 7. Investigation of shared miRNAs in two diseases and construction of the shared miRNAs mRNA network and Construction of the TF-key genes network. (**A**): Venn diagram showing the intersection of miRNAs associated with AD and PD. (**B**): miRNAs-mRNAs network. (**C**): TF-key genes network.

3.8. Construction of the TF-Key Genes Network

Based on the TTRUST database, 6 transcription factors (TFs) were identified that regulate the hub genes. The identified TFs are NFKB1, RELA, IRF1, EP300, JUN, and IKBKB. The constructed TFs–hub genes network includes 6 TFs and 3 key genes: CD69, MMP9, and VCAM1 (Figure 7C). This network highlights the regulatory interactions between the TFs and the key hub genes, illustrating the complex regulatory mechanisms involved.

4. Discussion

Our comprehensive bioinformatics analysis identified 124 shared differentially expressed genes (DEGs) between AD and PD, with a focus on 13 key hub genes. We also identified 16 common miRNAs and constructed miRNAs-mRNAs and TFs-hub genes networks involving key miRNAs and transcription factors. One of the key biases in our study is the reliance on existing datasets from the GEO database, which may not represent all possible genetic variations. To mitigate this, we applied stringent inclusion criteria, focusing on human samples with consistent sequencing platforms and performing batch corrections using the "SVA" package in R. Despite many unclear mechanisms of AD, it is well-established that it is closely related to the immune system. Our integrative analysis identified shared transcriptomic signatures between AD and PD (124 DEGs, 13 hub genes, and 16 miRNAs) that map to immune and adhesion pathways. These findings suggest, but do not establish, common biology across the two conditions. Accordingly, the molecules prioritised here should be viewed as candidate markers and putative targets for follow-up rather than confirmed therapeutic targets. GO analysis indicated significant involvement in biological processes such as leukocyte migration, T cell activation, and response to bacterial origin molecules. Cellular component analysis highlighted significant enrichment in the external side of the plasma membrane, secretory granule membrane, and extracellular matrix. Molecular function analysis revealed significant enrichment in activities such as peptidase activity, enzyme activator activity, and carbohydrate binding. KEGG pathway enrichment analysis revealed several critical pathways, including cell adhesion molecules, lipid and atherosclerosis, and cytokine-cytokine receptor interaction. Notably, the NF-kappa B signaling pathway was significantly enriched, suggesting its crucial role in the inflammatory processes underlying both AD and PD [30].

Our results fit a tentative model in which NF-κB–linked inflammation coordinates cytokine production across tissues, adhesion programs (VCAM1) enable leukocyte trafficking, and matrix turnover (MMP9, PXDN) maintains tissue susceptibility; CD69 marks T-cell activation at this interface. This framework offers a biologically coherent rationale for overlap without implying that PD causes AD or vice versa. These observations are hypothesis-generating and nominate specific perturbations (e.g., VCAM1 blockade; MMP9/CD69 modulation) and prospective cohorts to test disease specificity and clinical relevance.

CD69+ T cells are integral to the immune response in periodontal disease. In patients with chronic periodontal disease, CD69+ T regulatory (Treg) cells are elevated in peripheral blood compared to healthy individuals. However, these cells exhibit diminished suppressive function, suggesting an impaired regulatory role that contributes to disease progression [31]. In atopic dermatitis, CD69 expression is linked to allergic inflammation. CD69-deficient mice show enhanced inflammatory responses in asthma and contact hypersensitivity models, indicating that CD69 acts as a negative regulator of allergen-induced T-cell effector responses [32]. Additionally, staphylococcal exotoxins, common in AD, can upregulate CD69 expression on eosinophils, suggesting a modulatory role in the allergic inflammatory response in AD [33]. Thus, CD69 is pivotal in both diseases, regulating T-cell responses and contributing to inflammatory processes, highlighting its therapeutic potential.

Matrix metalloproteinase-9 (MMP9) is crucial in degrading extracellular matrix components, significantly impacting inflammatory processes in both periodontal disease and atopic dermatitis. In periodontal disease, MMP9's elevated levels in the gingival tissues of chronic periodontitis patients contribute to collagen and extracellular matrix breakdown, exacerbating tissue destruction and disease progression [34]. The expression of MMP9 is influenced by genetic polymorphisms and inflammatory cytokines, indicating its complex role in tissue degradation [35]. Similarly, in atopic dermatitis, elevated MMP9 levels are observed in skin lesions, correlating with disease severity and contributing to chronic inflammation and tissue remodeling [36]. Therefore, MMP9 is essential in both conditions, contributing to tissue destruction and inflammation, making it a valuable target for therapeutic intervention.

Vascular cell adhesion molecule-1 (VCAM1) is critical in the inflammatory processes of both periodontal disease and atopic dermatitis. It facilitates immune cell migration and inflammation by promoting leukocyte adhesion to endothelial cells. In periodontal disease, VCAM1 genetic polymorphisms, such as rs1041163, are associated with increased susceptibility and severity of chronic periodontitis, indicating its role in periodontal tissue destruction [37]. VCAM1 promotes leukocyte adhesion and migration into periodontal tissues, exacerbating inflammation and tissue breakdown. In atopic dermatitis, VCAM1 is significantly upregulated in lesional and non-

lesional skin, contributing to chronic inflammation. Studies have shown that blocking VCAM1 can delay dermatitis onset and reduce disease severity in animal models, indicating its critical role in AD pathogenesis [38]. Elevated levels of soluble VCAM1 in the serum of AD patients correlate with disease activity, further emphasizing its role in AD [39]. Thus, VCAM1 is a key molecule in both conditions, promoting inflammatory responses by mediating immune cell adhesion and migration, suggesting its potential as a therapeutic target.

Peroxidasin (PXDN) is crucial in tissue remodeling and inflammatory processes in both periodontal disease and atopic dermatitis. It contributes to forming cross-links in the extracellular matrix, essential for tissue integrity and immune response modulation. In periodontal disease, PXDN is involved in the oxidative modification of the extracellular matrix, influencing tissue remodeling and inflammation. Chronic periodontitis is characterized by an imbalance in the production and degradation of extracellular matrix components, leading to tissue destruction and disease progression. PXDN's role in promoting oxidative stress and inflammation is key in periodontal tissue damage [40]. Similarly, in atopic dermatitis, PXDN is significantly upregulated in inflamed skin tissues, involved in forming extracellular matrix components essential for skin barrier function and wound healing. PXDN's role in tissue remodeling and inflammation makes it a critical player in the chronic inflammatory response seen in AD. Increased PXDN expression is linked to enhanced tissue repair processes and modulation of inflammatory responses in the skin, crucial for managing AD symptoms [41]. Overall, PXDN is a key enzyme in both conditions, contributing to tissue remodeling and inflammation, underscoring its potential as a therapeutic target for managing these chronic inflammatory diseases.

The genes CD69, MMP9, VCAM1, and PXDN exhibit overlapping roles in both atopic dermatitis and periodontal disease, primarily by influencing inflammatory processes and tissue remodeling. CD69 regulates T-cell responses and inflammatory processes in both diseases. MMP9 contributes to tissue destruction through extracellular matrix degradation, exacerbating inflammation. VCAM1 facilitates immune cell adhesion and migration, driving inflammatory responses. PXDN is involved in the oxidative modification of the extracellular matrix, essential for tissue integrity and immune response modulation. The shared involvement of these genes in immune regulation and inflammation highlights potential common therapeutic targets for both conditions, offering a promising avenue for developing treatments that address both AD and PD simultaneously.

After identifying four key genes (CD69, MMP9, PXDN, VCAM1), we used the HMDD database to determine 16 shared miRNAs in AD and PD. We then constructed a miRNA-mRNA network, highlighting the interactions between these miRNAs and the key genes PXDN, MMP9, and VCAM1. Specifically, hsa-miR-9-5p, hsa-miR-21-5p, hsa-miR-143-3p, and hsa-miR-155-5p play significant roles in regulating biological processes such as inflammation, immune response, and tissue remodeling.

Using the TRRUST database, we identified six transcription factors (NFKB1, RELA, IRF1, EP300, JUN, IKBKB) that regulate the expression of key genes. These transcription factors also play crucial roles in inflammation and immune responses in AD and PD. Among them, NFKB1 and RELA are core components of the NF-κB signaling pathway [42]. This pathway has been demonstrated in multiple studies to be critical in regulating the occurrence of periodontitis and atopic dermatitis [43,44].

NFKB1 (p50) and RELA (p65) are important members of the NF-κB family. NFKB1 participates in inflammation and immune regulation by regulating the expression of downstream genes such as cytokines, chemokines, and adhesion molecules [45]. RELA promotes the production of inflammatory mediators such as TNF-α, IL-1β, and IL-6 by activating gene expression, thus contributing to both acute and chronic inflammatory responses [46].

Interestingly, three of the four miRNAs identified in the miRNA-mRNA network (hsa-miR-21-5p, hsa-miR-143-3p, and hsa-miR-155-5p) directly or indirectly affect the NF-κB signaling pathway. hsa-miR-21-5p indirectly activates the NF-κB signaling pathway by targeting PTEN, PDCD4, and SPRY1, thereby enhancing inflammatory responses [47]. miR-143-3p has been found to regulate the TLR4/MyD88/NF-κB pathway, reducing the expression of inflammatory factors and cell apoptosis [48]. hsa-miR-155-5p amplifies NF-κB signaling by inhibiting negative regulators of the NF-κB pathway, thus promoting cell survival and proliferation [49].

Although numerous studies have shown that both diseases are related to the NF-κB pathway, most of these studies focus only on the terminal stages of the NF-κB pathway. Our approach, from the perspective of miRNAs and transcription factors, reveals shared molecular mechanisms in AD and PD. These findings not only highlight the critical roles of miRNAs and TFs in inflammation and immune responses but also suggest their potential as therapeutic targets. The shared signatures identified here arise from cross-tissue comparisons (skin in AD; gingival/periodontal tissues in PD) and should therefore be interpreted with caution. While convergence on immune and adhesion pathways—including NF-κB–related processes—is consistent with biology implicated in both conditions, our integrative approach cannot establish causality, determine directionality (e.g., whether one disease predisposes to the other), or demonstrate clinical utility. Differences in tissue context, sample handling,

and unmeasured confounding (age, sex, smoking, comorbidities, and medication use) may contribute to the observed overlap. In addition, this study relied on public datasets without experimental validation; analyses used local tissues rather than blood; sample-size imbalance (fewer AD samples) and platform heterogeneity may have affected DEG detection. The work was restricted to the transcriptome and lacked individual-level covariates, limiting generalizability and precluding adjustment for confounders. Overall, these caveats frame the results as hypothesis-generating and motivate functional studies in relevant cell types, validation in independent, prospective cohorts, and integration of multi-omics data to delineate disease-specific versus shared mechanisms.

5. Conclusions

This study identified significant shared regulatory mechanisms between AD and PD through bioinformatics analysis. We identified 124 common differentially expressed genes (DEGs) and highlighted four key genes (CD69, MMP9, PXDN, VCAM1). These genes were validated for their diagnostic efficacy in both diseases. Our miRNA-mRNA network construction underscored the roles of hsa-miR-9-5p, hsa-miR-21-5p, hsa-miR-143-3p, and hsa-miR-155-5p in regulating inflammation, immune response, and tissue remodeling. Additionally, NFKB1, RELA, IRF1, EP300, JUN, and IKBKB were identified as key transcription factors regulating these genes and are crucial components of the NF-κB signaling pathway. Our findings suggest that this pathway contributes to the inflammatory processes in both diseases. Although previous studies have validated the involvement of the NF-κB signaling pathway in AD and PD separately, our research connects the key pathways of these two diseases through genes, miRNAs, and TFs. These findings not only highlight the critical roles of miRNAs and TFs in inflammation and immune responses but also suggest their potential as therapeutic targets. Further validation and experimental studies are essential to translate these findings into clinical applications, providing precise and effective treatment strategies for chronic diseases. By targeting these identified genes, miRNAs, and transcription factors, we can potentially improve therapeutic outcomes and more effectively manage the comorbidity of AD and PD.

Author Contributions

K.L.: conceptualization, formal analysis, investigation, methodology, and writing—original draft preparation; L.X.: formal analysis, investigation, methodology; G.G.: methodology, project administration; Y.Z.: conceptualization, investigation, and methodology; L.N.: conceptualization, methodology; C.L.: methodology, project administration, funding acquisition and writing—review and editing; Z.C.: conceptualization, methodology, supervision, project administration, funding acquisition and writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research was funded by Guangdong Basic and Applied Basic Research Foundation, grant number 2020A1515110409, and Guangzhou Basic and Applied Basic Research Foundation-Project for PilotVoyage, grant number 2024A04J6323.

Institutional Review Board Statement

Ethical review and approval were waived for this study because all data were obtained from publicly available, de-identified human transcriptomic datasets in the NCBI GEO database. No new human or animal subjects were involved in this research.

Informed Consent Statement

Not applicable. This study analyzed publicly available, de-identified transcriptomic datasets from the NCBI GEO database; no new human participants were recruited or directly involved.

Data Availability Statement

All data analyzed in this study are publicly available from the NCBI Gene Expression Omnibus (GEO) under accession numbers GSE16134, GSE23586, GSE120721, and GSE182740. Validation datasets included GSE10334 (periodontitis) and GSE130588 (atopic dermatitis). Processed data and analysis scripts are available from the corresponding authors upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) for English language polishing and grammar improvement. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the final version of the manuscript.

References

1. Mayba, J.N.; Gooderham, M.J. Review of Atopic Dermatitis and Topical Therapies. *J. Cutan. Med. Surg.* **2017**, *21*, 227–236. https://doi.org/10.1177/1203475416685077.
2. Weidinger, S.; Beck, L.A.; Bieber, T.; et al. Atopic dermatitis. *Nat. Rev. Dis. Primers* **2018**, *4*, 1. https://doi.org/10.1038/s41572-018-0001-z.
3. Thomsen, S.F. Atopic Dermatitis: Natural History, Diagnosis, and Treatment. *ISRN Allergy* **2014**, *2014*, 354250. https://doi.org/10.1155/2014/354250.
4. Mansouri, Y.; Guttman-Yassky, E. Immune Pathways in Atopic Dermatitis, and Definition of Biomarkers through Broad and Targeted Therapeutics. *J. Clin. Med.* **2015**, *4*, 858–873. https://doi.org/10.3390/jcm4050858.
5. DaVeiga, S.P. Epidemiology of atopic dermatitis: A review. *Allergy Asthma Proc.* **2012**, *33*, 227–234. https://doi.org/10.2500/aap.2012.33.3569.
6. Silverberg, J.I.; Gelfand, J.M.; Margolis, D.J.; et al. Patient burden and quality of life in atopic dermatitis in US adults. *Ann. Allergy Asthma Immunol.* **2018**, *121*, 340–347. https://doi.org/10.1016/j.anai.2018.07.006.
7. Wang, A.; Xu Landén, N. New insights into T cells and their signature cytokines in atopic dermatitis. *IUBMB Life* **2015**, *67*, 601–610. https://doi.org/10.1002/iub.1405.
8. Nakajima, S.; Tie, D.; Nomura, T.; et al. Novel pathogenesis of atopic dermatitis from the view of cytokines in mice and humans. *Cytokine* **2021**, *148*, 155664. https://doi.org/10.1016/j.cyto.2021.155664.
9. Alsulami, S.; Aldoboke, A.; Nooh, R.; et al. Prevalence of Asthma, Allergic Rhinitis, and Atopic Dermatitis and Their Association With Oral Health in Saudi Arabia. *Cureus* **2023**, *15*, e38061. https://doi.org/10.7759/cureus.38061.
10. Smirnova, J.; Montgomery, S.; Lindberg, M.; et al. Associations of self-reported atopic dermatitis with comorbid conditions in adults: A population-based cross-sectional study. *BMC Dermatol.* **2020**, *20*, 23. https://doi.org/10.1186/s12895-020-00117-8.
11. Qasim, S.S.B.; Al-Otaibi, D.; Al-Jasser, R.; et al. An Evidence-Based Update on the Molecular Mechanisms Underlying Periodontal Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 3829. https://doi.org/10.3390/ijms21113829.
12. Uesaka, K.; Oka, H.; Kato, R.; et al. Bioinformatics in bioscience and bioengineering: Recent advances, applications, and perspectives. *J. Biosci. Bioeng.* **2022**, *134*, 363–373. https://doi.org/10.1016/j.jbiosc.2022.08.004.
13. Werfel, T.; Allam, J.-P.; Biedermann, T.; et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J. Allergy Clin. Immunol.* **2016**, *138*, 336–349. https://doi.org/10.1016/j.jaci.2016.06.010.
14. Genco, R.J.; Van Dyke, T.E. Reducing the risk of CVD in patients with periodontitis. *Nat. Rev. Cardiol.* **2010**, *7*, 479–480. https://doi.org/10.1038/nrcardio.2010.120.
15. Kebschull, M.; Demmer, R.T.; Papapanou, P.N. "*Gum Bug, Leave My Heart Alone*!"—Epidemiologic and Mechanistic Evidence Linking Periodontal Infections and Atherosclerosis. *J. Dent. Res.* **2010**, *89*, 879–902. https://doi.org/10.1177/0022034510375281.
16. Corbella, S.; Veronesi, P.; Galimberti, V.; et al. Is periodontitis a risk indicator for cancer? A meta-analysis. *PLoS ONE* **2018**, *13*, e0195683. https://doi.org/10.1371/journal.pone.0195683.
17. Bingham, C.O.; Moni, M. Periodontal disease and rheumatoid arthritis: The evidence accumulates for complex pathobiologic interactions. *Curr. Opin. Rheumatol.* **2013**, *25*, 345–353. https://doi.org/10.1097/BOR.0b013e32835fb8ec.
18. Preshaw, P.M.; Alba, A.L.; Herrera, D.; et al. Periodontitis and diabetes: A two-way relationship. *Diabetologia* **2012**, *55*, 21–31. https://doi.org/10.1007/s00125-011-2342-y.
19. Simpson, T.C.; Clarkson, J.E.; Worthington, H.V.; et al. Treatment of periodontitis for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst. Rev.* **2022**, *4*. https://doi.org/10.1002/14651858.CD004714.pub4.
20. Barrett, T.; Wilhite, S.E.; Ledoux, P.; et al. NCBI GEO: Archive for functional genomics data sets—Update. *Nucleic Acids Res.* **2012**, *41*, D991–D995. https://doi.org/10.1093/nar/gks1193.
21. Szklarczyk, D.; Gable, A.L.; Lyon, D.; et al. STRING v11: Protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res.* **2019**, *47*, D607–D613. https://doi.org/10.1093/nar/gky1131.
22. Bader, G.D.; Hogue, C.W. An automated method for finding molecular complexes in large protein interaction networks. *BMC Bioinform.* **2003**, *4*, 2. https://doi.org/10.1186/1471-2105-4-2.
23. Chin, C.-H.; Chen, S.-H.; Wu, H.-H.; et al. *cytoHubba*: Identifying hub objects and sub-networks from complex interactome. *BMC Syst. Biol.* **2014**, *8*, S11. https://doi.org/10.1186/1752-0509-8-S4-S11.

24. Shen, Y.; Gao, Y.; Shi, J.; et al. MicroRNA–Disease Network Analysis Repurposes Methotrexate for the Treatment of Abdominal Aortic Aneurysm in Mice. *Genom. Proteom. Bioinform.* **2023**, *21*, 1030–1042. https://doi.org/10.1016/j.gpb.2022.08.002.
25. Lu, M.; Zhang, Q.; Deng, M.; et al. An Analysis of Human MicroRNA and Disease Associations. *PLoS ONE* **2008**, *3*, e3420. https://doi.org/10.1371/journal.pone.0003420.
26. Cui, C.; Zhong, B.; Fan, R.; et al. HMDD v4.0: A database for experimentally supported human microRNA-disease associations. *Nucleic Acids Res.* **2024**, *52*, D1327–D1332. https://doi.org/10.1093/nar/gkad717.
27. Huang, H.-Y.; Lin, Y.-C.-D.; Cui, S.; et al. miRTarBase update 2022: An informative resource for experimentally validated miRNA–target interactions. *Nucleic Acids Res.* **2022**, *50*, D222–D230. https://doi.org/10.1093/nar/gkab1079.
28. Li, J.; Han, X.; Wan, Y.; et al. TAM 2.0: Tool for MicroRNA set analysis. *Nucleic Acids Res.* **2018**, *46*, W180–W185. https://doi.org/10.1093/nar/gky509.
29. Han, H.; Cho, J.-W.; Lee, S.; et al. TRRUST v2: An expanded reference database of human and mouse transcriptional regulatory interactions. *Nucleic Acids Res.* **2018**, *46*, D380–D386. https://doi.org/10.1093/nar/gkx1013.
30. Yang, G.; Seok, J.K.; Kang, H.C.; et al. Skin Barrier Abnormalities and Immune Dysfunction in Atopic Dermatitis. *Int. J. Mol. Sci.* **2020**, *21*, 2867. https://doi.org/10.3390/ijms21082867.
31. Vitales-Noyola, M.; Martínez-Martínez, R.; Loyola-Rodríguez, J.P.; et al. Quantitative and functional analysis of CD 69 + T regulatory lymphocytes in patients with periodontal disease. *J. Oral Pathol. Med.* **2017**, *46*, 549–557. https://doi.org/10.1111/jop.12514.
32. Martín, P.; Gómez, M.; Lamana, A.; et al. The leukocyte activation antigen CD69 limits allergic asthma and skin contact hypersensitivity. *J. Allergy Clin. Immunol.* **2010**, *126*, 355–365.e3. https://doi.org/10.1016/j.jaci.2010.05.010.
33. Wedi, B.; Wieczorek, D.; Stünkel, T.; et al. Staphylococcal exotoxins exert proinflammatory effects through inhibition of eosinophil apoptosis, increased surface antigen expression (CD11b, CD45, CD54, and CD69), and enhanced cytokine-activated oxidative burst, thereby triggering allergic inflammatory reactions. *J. Allergy Clin. Immunol.* **2002**, *109*, 477–484. https://doi.org/10.1067/mai.2002.121702.
34. Smith, P.C.; Muñoz, V.C.; Collados, L.; et al. *In situ* detection of matrix metalloproteinase-9 (MMP-9) in gingival epithelium in human periodontal disease. *J. Periodontal Res.* **2004**, *39*, 87–92. https://doi.org/10.1111/j.1600-0765.2004.00705.x.
35. Kumar, M.S.; Vamsi, G.; Sripriya, R.; et al. Expression of Matrix Metalloproteinases (MMP-8 and -9) in Chronic Periodontitis Patients With and Without Diabetes Mellitus. *J. Periodontol.* **2006**, *77*, 1803–1808. https://doi.org/10.1902/jop.2006.050293.
36. Valenzuela, F.; Fernández, J.; Aroca, M.; et al. Gingival Crevicular Fluid Zinc- and Aspartyl-Binding Protease Profile of Individuals with Moderate/Severe Atopic Dermatitis. *Biomolecules* **2020**, *10*, 1600. https://doi.org/10.3390/biom10121600.
37. Wang, L.; Li, X.-H.; Ning, W.-C. Evaluation of ICAM-1 and VCAM-1 Gene Polymorphisms in Patients with Periodontal Disease. *Med. Sci. Monit.* **2016**, *22*, 2386–2391. https://doi.org/10.12659/MSM.896979.
38. Chen, L.; Lin, S.; Amin, S.; et al. VCAM-1 blockade delays disease onset, reduces disease severity and inflammatory cells in an atopic dermatitis model. *Immunol. Cell Biol.* **2010**, *88*, 334–342. https://doi.org/10.1038/icb.2009.107.
39. Marinović Kulišić, S.; Takahashi, M.; Himelreich Perić, M.; et al. Immunohistochemical Analysis of Adhesion Molecules E-Selectin, Intercellular Adhesion Molecule-1, and Vascular Cell Adhesion Molecule-1 in Inflammatory Lesions of Atopic Dermatitis. *Life* **2023**, *13*, 933. https://doi.org/10.3390/life13040933.
40. Liu, Y.; Wang, Z.; Jiang, W.; et al. Systemic Type 2 Inflammation-Associated Atopic Dermatitis Exacerbates Periodontitis. *Int. Arch. Allergy Immunol.* **2024**, *185*, 84–98. https://doi.org/10.1159/000533434.
41. Jiménez, C.; Fernández, J.; Aroca, M.; et al. Association of Periodontitis and Atopic Dermatitis with the Levels of IL-13, IL-31, and TSLP in the Gingival Crevicular Fluid. *Int. J. Mol. Sci.* **2023**, *24*, 15592. https://doi.org/10.3390/ijms242115592.
42. Gilmore, T.D. The Rel/NF-κB signal transduction pathway: Introduction. *Oncogene* **1999**, *18*, 6842–6844. https://doi.org/10.1038/sj.onc.1203237.
43. Huber, M.A.; Denk, A.; Peter, R.U.; et al. The IKK-2/IκBα/NF-κB Pathway Plays a Key Role in the Regulation of CCR3 and eotaxin-1 in Fibroblasts. *J. Biol. Chem.* **2002**, *277*, 1268–1275. https://doi.org/10.1074/jbc.M109358200.
44. Kumar, A.; Mahendra, J.; Mahendra, L.; et al. Synergistic Effect of Biphasic Calcium Phosphate and Platelet-Rich Fibrin Attenuate Markers for Inflammation and Osteoclast Differentiation by Suppressing NF-κB/MAPK Signaling Pathway in Chronic Periodontitis. *Molecules* **2021**, *26*, 6578. https://doi.org/10.3390/molecules26216578.
45. Lawrence, T. The Nuclear Factor NF-B Pathway in Inflammation. *Cold Spring Harb. Perspect. Biol.* **2009**, *1*, a001651. https://doi.org/10.1101/cshperspect.a001651.
46. Perkins, N.D. Integrating cell-signalling pathways with NF-κB and IKK function. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 49–62. https://doi.org/10.1038/nrm2083.
47. Mao, X.; Chen, M.; Wang, Y.; et al. MicroRNA-21 regulates the ERK/NF-κB signaling pathway to affect the proliferation, migration, and apoptosis of human melanoma A375 cells by targeting SPRY1, PDCD4, and PTEN. *Mol. Carcinog.* **2017**, *56*, 886–894. https://doi.org/10.1002/mc.22542.

48. Wang, Y.; Li, H.; Shi, Y.; et al. miR-143-3p impacts on pulmonary inflammatory factors and cell apoptosis in mice with mycoplasmal pneumonia by regulating TLR4/MyD88/NF-κB pathway. *Biosci. Rep.* **2020**, *40*, BSR20193419. https://doi.org/10.1042/BSR20193419.
49. Jablonska, E.; Gorniak, P.; Prusisz, W.; et al. MiR-155 Amplifies AKT and NFkB Signaling By Targeting Multiple Regulators of BCR Signal in DLBCL. *Blood* **2015**, *126*, 2455. https://doi.org/10.1182/blood.V126.23.2455.2455.