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RESEARCH

Integrated Genome-wide Association and Single-cell Transcriptomic Analysis Identifies OAT as Therapeutic Targets for Periodontitis

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Abstract

Periodontitis is a chronic inflammatory disease affecting tooth-supporting tissues. Beyond microbial dysbiosis, host metabolic regulation plays a critical role. This study identified ornithine aminotransferase (OAT), a mitochondrial enzyme in amino acid metabolism, as associated with altered fibroblast phenotypes and metabolic profiles in periodontitis. Integrative genetic analysis showed a putative causal relationship between increased OAT expression and disease risk. Single-cell RNA-Seq revealed OAT enrichment in fibroblasts, especially in subsets with inflammatory and matrix-remodeling characteristics. In diseased tissues, OAT-positive fibroblasts exhibited heightened metabolic activity and acted as central nodes in intercellular communication with immune and endothelial cells. Pseudotime analysis indicated progressive downregulation of OAT during fibroblast differentiation. OAT expression correlated with activation of arginine and proline metabolism, implicating a role in sustaining inflammation and matrix degradation. These results suggest that OAT contributes to periodontal tissue damage and may serve as a therapeutic target.

Keywords Periodontitis · Mendelian randomization · Ornithine aminotransferase · Single-cell RNA-Seq

Introduction

Periodontitis is a chronic inflammatory and metabolic disorder initiated by oral biofilms. It leads to progressive destruction of the tooth-supporting structures and is linked to systemic health complications [1, 2]. Epidemiological studies estimate that severe periodontitis affects approximately 11.2% of the global population [3]. Current treatment strategies primarily include scaling and root planing (SRP), surgical intervention, and antimicrobial therapies [4]. SRP is effective in the early stages but becomes less predictable in advanced or anatomically complex cases [5]. Surgical procedures provide access to deeper lesions but often yield variable outcomes depending on disease severity and patient factors [6]. While systemic antibiotics can improve treatment outcomes, their use is limited by adverse effects and antimicrobial resistance [7]. In contrast, local antimicrobials offer targeted delivery but are expensive and require repeated dosing [8]. Notably, these conventional approaches primarily manage symptoms without addressing the root causes, often resulting in disease recurrence.

Growing evidence indicates that genetic predisposition significantly influences an individual's risk of developing periodontitis, as well as the severity and progression of the disease [9]. Although bacterial biofilms act as the primary trigger for inflammation, the host's genetic makeup plays a central role in shaping immune responses and tissue remodeling [10, 11]. Genetic variations in key regulators of inflammation—such as cytokines (IL-1, IL-6, IL-10), pattern recognition receptors including Toll-like and Fcγ receptors, as well as tissue-degrading enzymes like matrix metalloproteinases and COX-2—have been linked to individual differences in disease severity and bone loss [12–14].

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These mediators are regulated by genetic factors. Identifying relevant gene polymorphisms could help explain individual susceptibility to periodontitis and promote personalized therapies that target the biological mechanisms of disease rather than just alleviating symptoms [15].

To explore novel therapeutic avenues for periodontitis, we integrated genome-wide association study (GWAS) data with blood expression quantitative trait loci (eQTL) information, employing a stepwise analytical framework. This comprehensive pipeline encompassed Mendelian randomization (MR), colocalization analysis, phenome-wide association studies (PheWAS), enrichment analysis, single-cell RNA-Seq, drug repurposing prediction, and molecular docking. Through this approach, we identified genetic loci potentially associated with disease susceptibility, aiming to facilitate the development of more precise and effective therapeutic strategies for periodontitis.

Methods

The overall workflow of this study was presented in Fig. 1.

Exposure Data

Druggable genes were identified from two sources: the Drug-Gene Interaction Database (DGIdb, https://www.dgidb.org/) [16] and a curated list by Finan et al. [17], resulting in a combined set of 5,883 genes [18]. Cis-eQTLs were obtained from the eQTLGen consortium [19], which includes data on 16,987 genes derived from 31,684 blood samples of individuals of European ancestry. By intersecting these datasets, a total of 3,275 genes were retained and designated as the exposure variables for the present study.

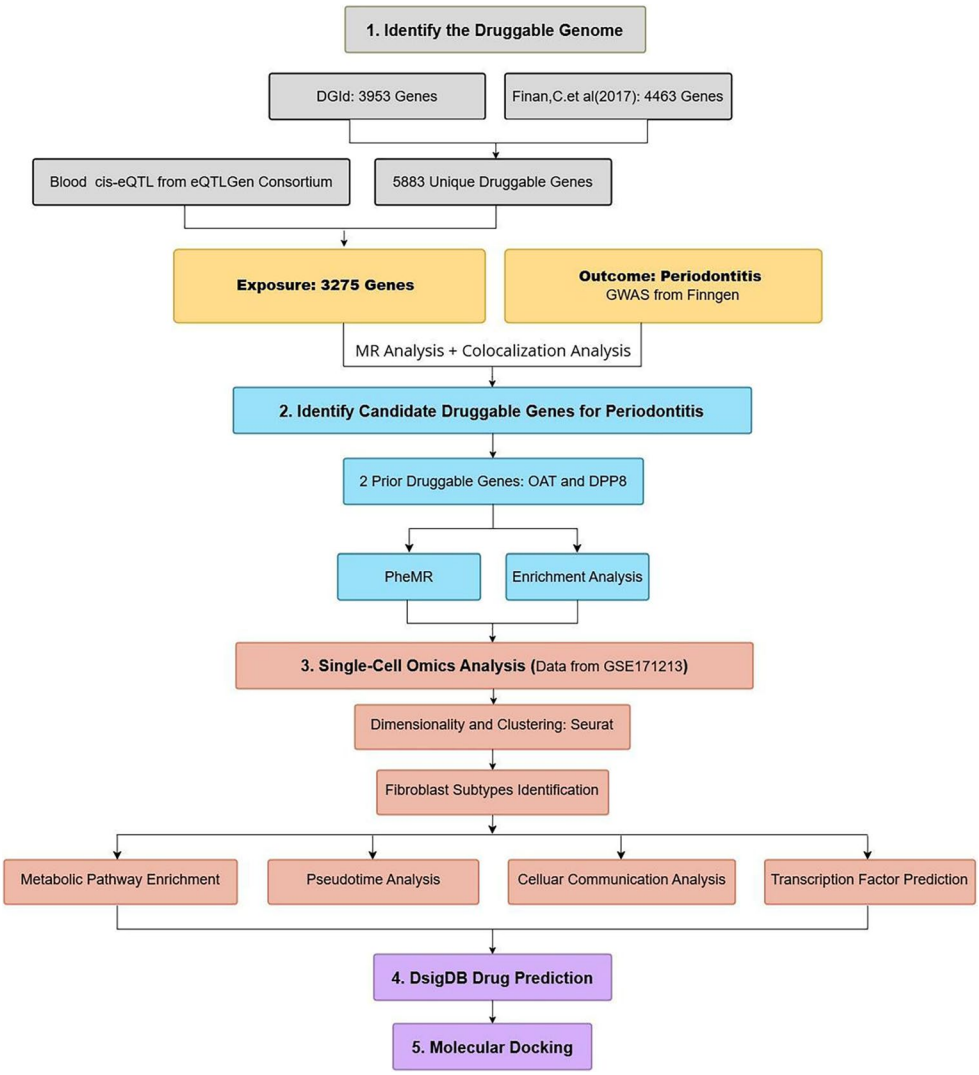

Fig. 1 Flow chart of this study design.

Outcome Data

Genetic summary statistics for periodontitis were obtained from FINNGEN 11, last updated on June 24, 2024. The dataset included 406,876 individuals of European ancestry, with 118,404 cases and 288,472 controls [20].

MR Analysis and Colocalization Analysis

MR analyses were conducted using the R package TwoSampleMR (version 0.6.6) [21], with cis-eQTLs of FDR (False Discovery Rate) < 0.05 within ± 100 kb of each gene's transcription start site selected as exposure instruments. SNPs (single-nucleotide polymorphism) were clumped based on linkage disequilibrium (r^2 = 0.20, window = 10,000 kb) [22], to retain a broader set of variants and increase statistical power, as adopted in previous MR study [23]. SNPs were harmonized with outcome data, and assessed for strength using F-statistics (threshold > 10) [24]. To account for pleiotropy, five MR methods were applied: inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode [25]. Consistent findings across methods were considered robust. Heterogeneity and causal direction were evaluated using Cochran's Q and the Steiger test, respectively [26].

To account for potential confounding when a single SNP is associated with multiple genes, colocalization analysis was conducted to assess whether periodontitis and gene expression share a causal variant. For genes with significant MR signals, the R package COLOC (v5.2.3) [27] was used with default prior probabilities (p1 = 1e − 4, p2 = 1e − 4, p12 = 1e − 5) [28]. In this framework, p1 indicates the probability of association with periodontitis, p2 with gene expression, and p12 with both traits. Five hypotheses were tested: PPH0 (no association with either trait), PPH1 (association with gene expression only), PPH2 (association with periodontitis only), PPH3 (both traits associated but with distinct causal variants), and PPH4 (both traits associated and sharing a single causal variant). A high PPH4 value (typically > 0.9) was interpreted as strong evidence of colocalization, suggesting a shared genetic mechanism underlying both traits.

Phenome-wide MR Analysis

To assess horizontal pleiotropy and potential side effects of candidate drug targets, a phenome-wide association study was performed using the AstraZeneca PheWAS Portal (https://azphewas.com/, software 28, Data Public 5.4, accessed 23 May 2024), based on data from 450,000 UK Biobank participants across 15,500 binary and 1,500 continuous phenotypes. A significance threshold of 2E − 9 was applied, following the portal's default multiple testing correction [29].

Enrichment Analysis

To explore the functional roles of the identified genes, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the clusterProfiler package (version 4.12.6) [30].

GO enrichment analysis was performed using the enrichGO function, with the org.Hs.eg.db database and ontology set to BP (Biological Process), CC (Cellular Component), and MF (Molecular Function). Significance thresholds were set at p-value < 0.05 and q-value < 0.05. Multiple testing correction was applied using the Benjamini–Hochberg method. KEGG enrichment analysis was conducted using enrichKEGG with organism = "hsa", keyType = "kegg", and the same p-value and q-value cutoffs. The FDR method was used for multiple testing correction. Enriched pathways were identified and visualized using dot plots.

Single-cell Transcriptome Processing

The publicly available single-cell RNA sequencing dataset GSE171213 was obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). This dataset comprises periodontal tissue samples from four healthy individuals and five untreated periodontitis patients. For downstream analysis, we used the 'Seurat' R package (version 4.3.0.1) [31], applying a stringent quality control approach: cells with fewer than 200 or more than 5,000 detected genes, fewer than 1,000 or more than 25,000 UMI counts, or greater than 20% mitochondrial gene content were excluded. Genes detected in fewer than 3 cells were also removed. Doublets were identified using the 'DoubletFinder' R package (version 2.0.4) [32], while RNA contamination was removed at the single-cell level using the 'DecontX' R package (version 1.0.0) [33].

To perform dimensionality reduction, we first identified the top 2000 most variable genes with the FindVariableFeatures function and scaled the data using ScaleData. Principal component analysis (PCA) was conducted on these variable genes, selecting the top 20 principal components to compute the neighborhood structure with FindNeighbors. To correct for batch effects across samples, we applied the Harmony algorithm. Clustering was performed using Seurat's graph-based approach (FindNeighbors and FindClusters), and a resolution of 0.7 was selected based on cluster stability assessments using the clustree package. UMAP was applied to the Harmony-corrected embeddings for visualization.

Subsequently, the expression profiles of target genes across the identified cell types were examined using the scplotter package (version 0.1.0) [34].

Gene Set Enrichment Analysis (GSEA)

We initially performed GSEA on each cell subtype using the REACTOME gene sets from the msigdbr R package (version 7.5.1) [35, 36]. For each cluster, we considered the top 5 enriched pathways with an adjusted p-value below 0.05 as significant. UCell scoring was subsequently applied to these significant pathways, providing further validation of pathway activity at the single-cell level. To characterize fibroblast heterogeneity, fibroblast cells were subsetted from the full single-cell atlas and re-clustered using Seurat, with a resolution parameter set to 0.9, selected based on cluster stability assessed using the clustree R package (version 0.5.1). Cluster-specific marker genes were identified using both the COSG R package (version 0.9.0) and Seurat's FindAllMarkers function (min.pct = 0.25, logfc. threshold = 0.25). Cluster annotations were assigned by cross-referencing identified markers with well-established fibroblast subtype markers from published studies. Each cluster was subsequently interpreted based on pathway enrichment analyses to determine their likely biological roles like inflammatory, ECM (extracellular matrix) -producing, proliferative and so on. GO analyses were performed using the clusterProfiler R package (version 4.6.2). The top 50 upregulated genes (based on $\log_2$ fold change) for each fibroblast subtype were used as input. The enrichGO function was applied with the following parameters: keyType = "ENTREZID", OrgDb = org.Hs.eg.db, pvalueCutoff = 0.05, pAdjustMethod = "fdr", minGSSSize = 10, maxGSSSize = 500, and qvalueCutoff = 0.05. Results were visualized using the SCP R package (version 0.5.6) [37].

To explore metabolic pathway enrichment specifically within OAT + and OAT- fibroblast subpopulations, we employed the irGSEA R package (version 2.1.5) [38] alongside curated metabolic pathways from the scMetabolism R package (version 0.2.1) [39], pathway scores were subsequently correlated with OAT expression levels to assess the relationship between OAT expression and pathway-specific metabolic activity, providing insights into the metabolic adaptations within fibroblast subtypes in the context of OAT expression. In addition, pseudobulk analysis was performed by aggregating single-cell counts per sample using Seurat, followed by differential expression analysis with DESeq2 (version 1.42.0) [40]. Gene set enrichment was evaluated with fgsea (version 1.28.0) [41], and ssGSEA implemented in the GSVA R package (version 1.50.0) [42] was further applied to complement and validate the irGSEA results, consistently supporting the enrichment trend of the arginine and proline metabolism pathway.

Trajectory Analysis

To investigate fibroblast differentiation in disease progression, trajectory analysis was conducted using CytoTRACE (version 0.3.3) and monocle2 (version 2.26.0) [43]. CytoTRACE estimates cellular differentiation potential based on gene expression complexity (i.e., the number of expressed genes), where higher CytoTRACE scores indicate less differentiated or more immature cell states, and lower scores reflect more mature or differentiated cells. The CytoTRACE scores were projected onto the UMAP embedding to identify the most primitive fibroblast subpopulation, which was then assigned as the root state for pseudotime analysis in Monocle2. The Seurat object was first converted to a monocle object for pseudotime analysis. Differentially expressed genes were identified using differentialGeneTest (BH-corrected $P < 0.01$) to highlight key genes associated with fibroblast differentiation. Dimensionality reduction was then performed with the reduceDimension function using the DDRTree method, limited to two components. Cells were subsequently ordered along pseudotime using orderCells function with default parameters. Visualization of the trajectory and gene expression dynamics was achieved using R packages 'monocle2' and 'ggplot2' (version 3.5.1) [44].

Intercellular Communications Analysis

To compare cellular interactions between PD (Periodontitis) and HC (Healthy Control) samples, we performed intercellular communication analysis using the 'CellChat' R package (version 2.1.2) [45]. Annotated Seurat objects were converted to CellChat objects, and enriched ligands, receptors, and pathways were identified using identifyOverExpressedGenes and identifyOverExpressedInteractions. Results were compared between groups and visualized with 'CellChat' and 'ggplot2' R packages.

Transcription Factor Regulatory Network Analysis

Single-cell transcription factor (TF) regulatory network analysis was performed using pySCENIC (version 0.12.1). Subgroup-specific transcription factors were identified using the Wilcoxon rank-sum test. Gene coexpression analysis was initially conducted with the GRNBoost2 method implemented in the arboreto package (version 0.1.6) [46] to construct preliminary TF–target gene regulatory networks. Each coexpression module was subjected to cis-regulatory

motif enrichment analysis using the RcisTarget package (version 1.20.0) [47], and only modules containing target genes enriched for corresponding TF-binding motifs were retained to generate motif-validated regulons. Regulon activity was quantified at the single-cell level using AUCell (version 1.24.0), which scores the expression of each regulon's target genes in individual cells. Analysis and visualization were performed using the SCENIC (version 1.3.0) [47] and ggplot2 R packages.

Candidate Drug Prediction

Drug prediction analysis was performed using the Drug Signatures Database (DSigDB, http://dsigdb.tanlab.org/DSigDBv1.0/), which includes 22,527 gene sets and 17,389 compounds linked to 19,531 genes. Significant druggable genes identified earlier were used as input to predict potential therapeutic candidates based on drug-induced gene expression signatures [48].

Molecular Docking

Protein structures were retrieved from the Protein Data Bank and prepared in AutoDockTools (version 1.5.6) by removing water molecules, adding hydrogens, and assigning Gasteiger charges. Ligand structures were obtained from PubChem [49] database. Docking simulations were performed using AutoDock Vina 2.0 [50] to predict binding affinities and orientations within the target binding sites. Grid boxes were centered on co-crystallized ligand coordinates and adjusted to allow ligand flexibility. Docking results were visualized in PyMOL (version2.1.0), and binding affinities were evaluated based on predicted binding energies, with lower values indicating stronger interactions.

Statistical Analyses

All statistical analyses and graph generation were performed in R (version 4.3.2). Differences with p-values below 0.05 were regarded as statistically significant.

Results

Integrative Genomic Evidence Prioritizes OAT and DPP8 as Therapeutic Targets for Periodontitis

To investigate potential causal links between druggable genes and periodontitis, MR analysis was conducted on 3257 unique druggable genes (Tables S1–S4). Twelve genes reached FDR-adjusted significance (FDR < 0.05), indicating strong evidence for a potential causal association with periodontitis (Fig. 2A; Tables S5). Colocalization analysis showed that among the 12 previously identified significant genes, two genes—DPP8 and OAT—contained SNPs with PPH4 values exceeding 0.9. Both genes exhibited partial but notable colocalization with periodontitis (Fig. 2B, C; Table S6).

To evaluate whether the two identified candidate druggable genes influence other traits and to assess potential pleiotropy not captured by the MR-Egger intercept test, a PheWAS was performed using 17,361 binary and 1,419 quantitative phenotypes from the AstraZeneca PheWAS Portal. The results reflect associations between genetically predicted protein expression and a wide range of phenotypes. As shown in Fig. 2D-E and Tables S7–S10, neither DPP8 nor OAT exhibited significant associations with other traits. These findings suggest minimal off-target effects and a low risk of horizontal pleiotropy, further supporting the robustness of our results.

Enrichment Analysis Revealed the Biological Significance of the Potential Target Genes

GO enrichment analysis of the gene sets associated with OAT and DPP8 revealed functional involvement in several metabolic and enzymatic processes. In the BP category, significant enrichment was observed in glutamine family amino acid biosynthesis, proline metabolism, and arginine catabolism. For the CC, enrichment was primarily found in the mitochondrial matrix. In terms of MF, key terms included transferase activity (involving nitrogenous groups), transaminase activity, and dipeptidyl-peptidase activity (Fig. 2F).

To further investigate relevant signaling networks, KEGG pathway analysis revealed enrichment in the arginine and proline metabolism pathway (hsa00330), a key metabolic axis linked to inflammation and tissue remodeling (Fig. 2G).

Single-cell Transcriptomic Analysis Validates Expression Patterns of Target Genes

After stringent quality control, a total of 18,966 high-quality cells were retained. Based on canonical marker genes, these cells were classified into 15 transcriptionally distinct clusters and visualized using UMAP (Fig. 3A). These clusters were subsequently annotated based on canonical markers (Fig. 3B).

Differential expression analysis revealed distinct gene expression patterns across cell types. Notably, OAT was predominantly expressed in fibroblasts, while DPP8 showed upregulated expression in endothelial cells (Fig. 3C, D&

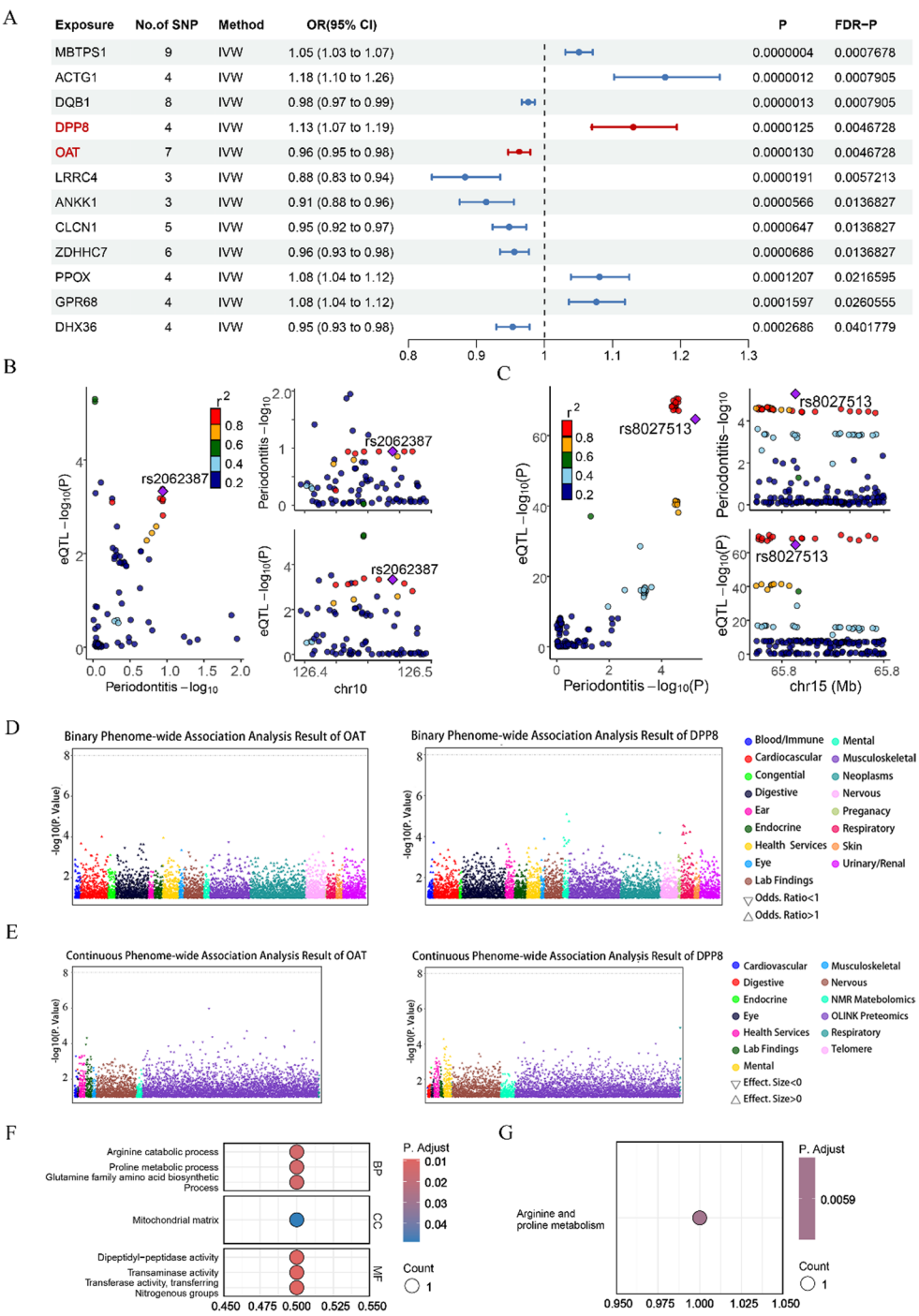

Fig. 2 Robust causal associations between OAT and DPP8 and periodontitis supported by multi-omics analyses. (**A**) Forest plot of 12 significant genes associated with periodontitis from blood. (**B-C**) Colocalization analysis result of OAT (B) and DPP8 (C) with periodontitis. Variants are colored by their r2 value, and the risk variant is labeled and uniquely colored purple. (**D-E**) Binary and continuous Phenome-wide association analysis result of OAT and DPP8. (F) The GO enrichment analysis results of OAT and DPP8. (G) The KEGG enrichment analysis results of OAT and DPP8.

Fig. S1A, B), suggesting that these genes may play roles within these cell populations. To further explore the functional characteristics of these cell clusters, we performed GSEA. Interestingly, as shown in Fig. 4A, UCell scoring for these pathways further validated the potential roles of fibroblasts, supporting their involvement in inflammation and tissue remodeling (Fig. 4B-D). Given the relatively low expression of DPP8, we subsequently focused our investigation on OAT.

Dynamic Expression and Functional Analysis of OAT in Fibroblast Subpopulations

Fibroblasts were isolated and classified into six transcriptionally distinct subtypes (Fib1–Fib6), which were distributed across both HC and PD samples, as illustrated in the UMAP plot (Fig. 5A, B). Although the total number of fibroblasts remained similar between HC and PD, there was a significant shift in the proportion of specific fibroblast

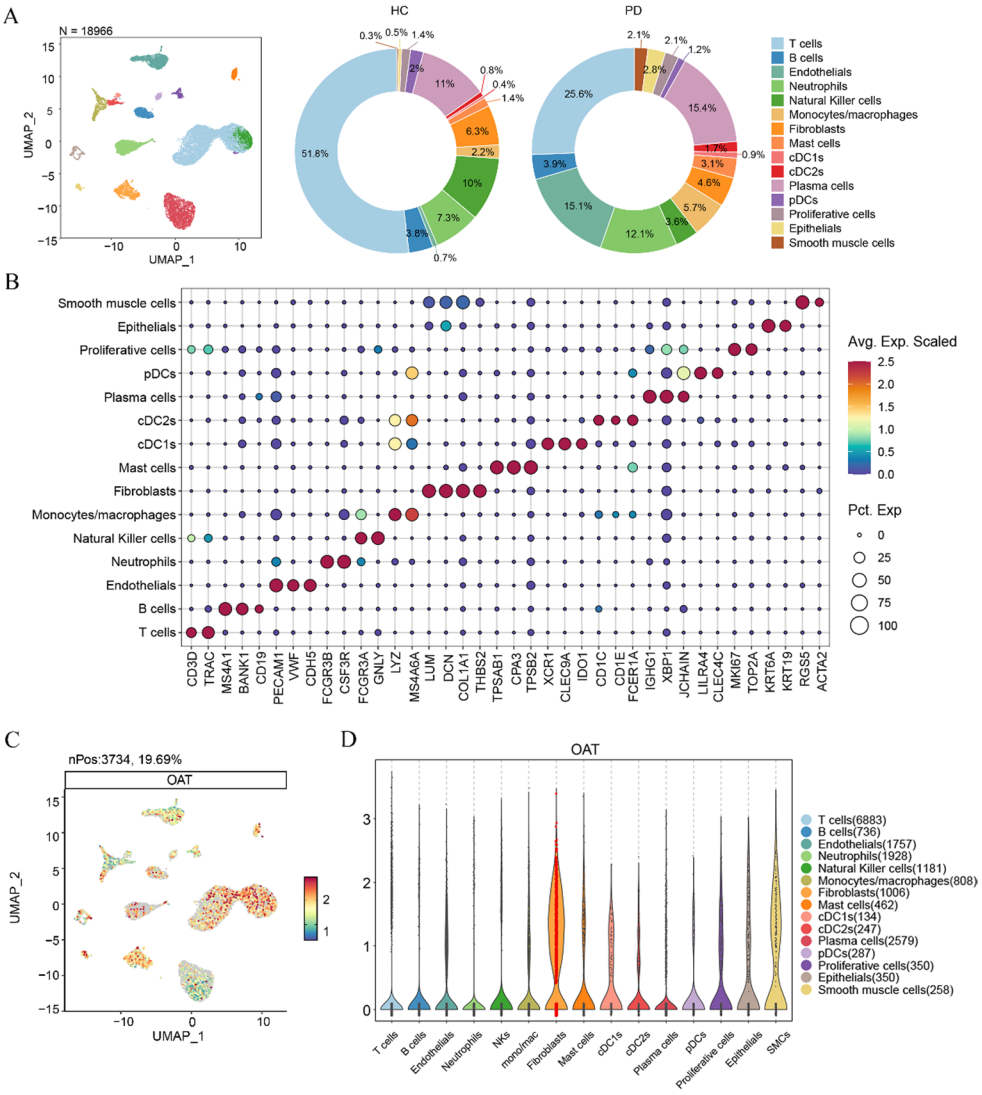

Fig. 3 Single-cell RNA-Seq analysis of target genes. (**A**) UMAP plots of 18, 966 cells after quality control and batch effect removal, colored by 15 distinct cell types and proportion of 15 major cell types showing in pie plots between HC and PD. Matched periodontal tissue samples were collected from healthy controls (n=4) and periodontitis patients (n=5). (**B**) Dot plot depicting the expression of canonical markers in major cell types. (**C**) Feature plots illustrating the expression patterns of OAT among different cell types, with color intensity indicating expression level. The percentage indicates the proportion of cells in that cluster expressing OAT. *nPos* refers to the number of OAT-positive cells within the cluster. (**D**) Violin plots demonstrating the OAT expression among different cell types.

subtypes: Fib2 and Fib3 were more prevalent in HC, whereas Fib1, Fib 4–6 were more prominent in PD patients (Fig. 5C). To explore the functional characteristics of each fibroblast subtype, we analyzed their enriched biological pathways. Fib1 and Fib4 were predominantly associated with inflammatory and immune-related functions, indicating roles in immune modulation. Fib2 and Fib3 were linked to ECM organization and structural maintenance, suggesting involvement in tissue integrity and support. Fib5 and Fib6 showed enrichment in developmental and proliferative processes, implying potential roles in cellular growth and differentiation (Fig. S2, S3).

Subsequent analysis of OAT expression revealed significantly higher OAT levels in PD patients compared to HC, particularly within inflammation-associated fibroblast subtypes (Fig. 5D). To elucidate the dynamic role of OAT during fibroblast differentiation, we further conducted a pseudotime trajectory analysis. Trajectory analysis provided valuable insights into fibroblast differentiation dynamics.

OAT expression exhibited a decreasing trend along the fibroblast differentiation trajectory. Both CytoTRACE and Monocle2 analyses consistently supported Fib6 as the developmental origin. We observed that OAT was most highly expressed in the less differentiated fibroblast subpopulations Fib1 and Fib6. As differentiation progressed toward ECM-producing and inflammation-associated subtypes (Fib3, Fib1, and Fib4), OAT expression gradually declined (Fig. 5E-I). This pattern suggests that OAT may play a role in maintaining an undifferentiated fibroblast state, or that its high expression serves as a marker of early developmental stages.

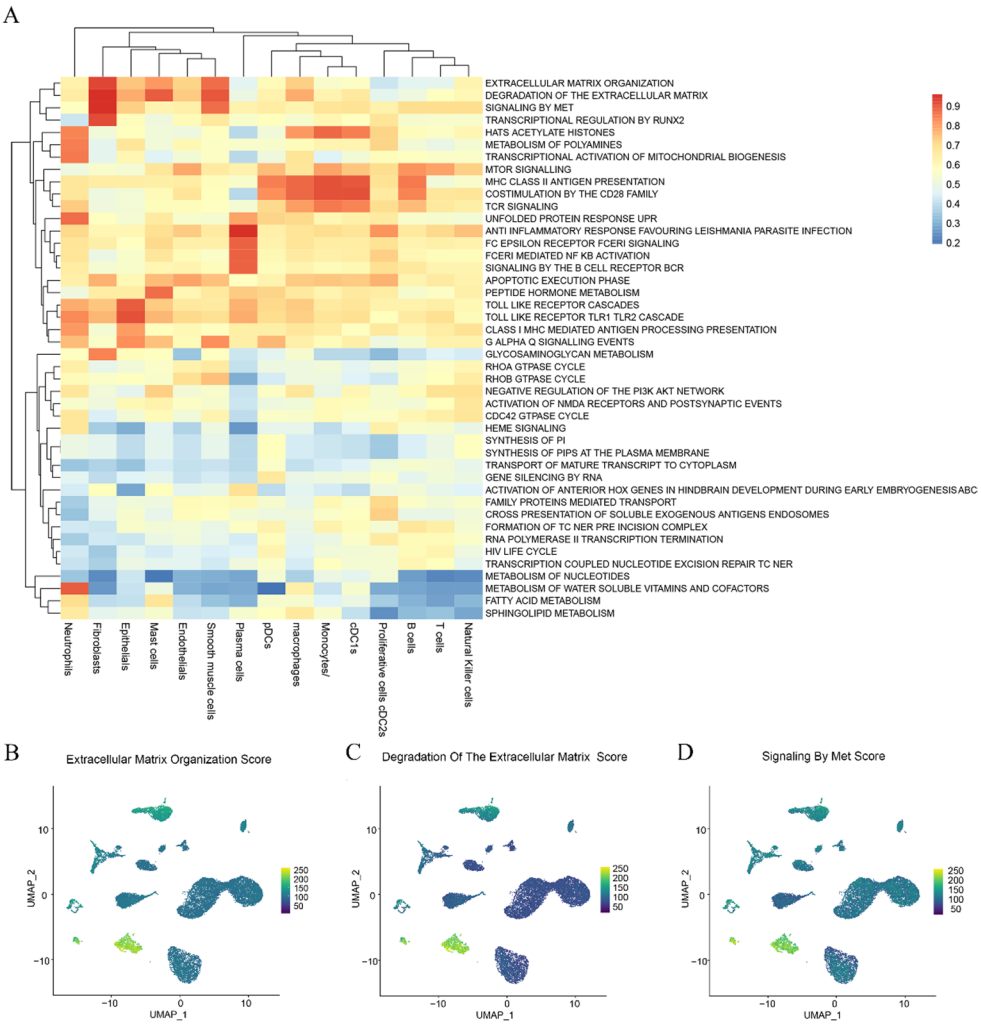

Fig. 4 GSEA and UCell scoring analysis. (**A**) The heatmap shows the top 5 enriched pathways for each cell cluster identified through GSEA, performed using the Reactome pathway database. (**B-D**) The UCell scoring analysis provides single-cell enrichment scores for key pathways identified through GSEA, including EXTRACELLULAR_MATRIX_ORGANIZATION, DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX, and SIGNALING_BY_MET.

Differential Metabolic Pathway Enrichment in OAT + and OAT- Fibroblasts

Given that OAT functions as a metabolism-related enzyme, its expression may modulate fibroblast activity via distinct metabolic pathways. Metabolic pathway activity was then assessed using the irGSEA R package just as in previous studies [51, 52], focusing on all metabolism-related pathways curated from the REACTOME databases, as defined by the scMetabolism R package.

Our analysis demonstrated significant upregulation of inflammation- and stress-related metabolic pathways in OAT+fibroblasts. In the REACTOME database, key enriched pathways included Arginine and proline metabolism, N-Glycan biosynthesis, and Glycolysis/Gluconeogenesis, with Arginine and proline metabolism being the most prominent. Similarly, KEGG pathway analysis highlighted Metabolism of polyamines, Nitric oxide metabolism (NOS3 activation), Amino acid metabolism, Glutamate and glutamine metabolism, and Glycogen metabolism as enriched in OAT+fibroblasts (Fig. 6A).

To further examine the relationship between OAT expression and these pathways, we conducted correlation analysis. OAT expression exhibited a positive correlation with both the arginine and proline metabolism pathway ($R = 0.42$, $p < 2.2e\text{-}16$) (Fig. 6B). These findings suggest that OAT may modulate fibroblast metabolic activities to enhance their adaptability for inflammatory responses and tissue repair in the pathogenesis of periodontitis. To validate these findings while properly accounting for between-sample variance, we performed a pseudobulk analysis by aggregating gene expression counts per sample using Seurat. Differential expression was conducted using DESeq2, followed by ranked gene set enrichment analysis using the fgsea R package. This sample-level analysis confirmed the key pathways identified by irGSEA, particularly the enrichment of arginine and proline metabolism in OAT$^+$ fibroblasts (Fig. 6C).

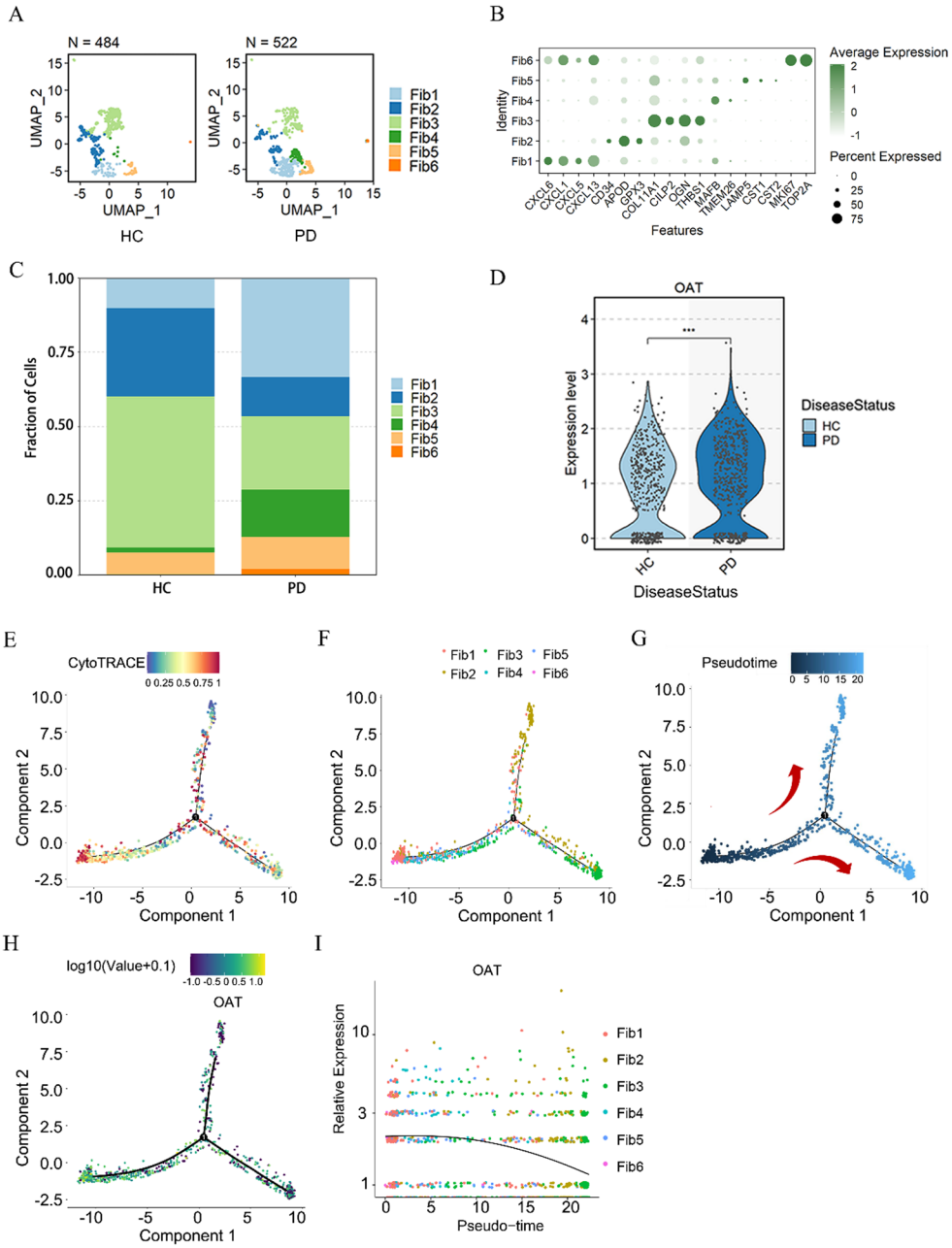

Fig. 5 Dynamic expression and functional implications of OAT in fibroblast subpopulations in periodontitis. (**A**) UMAP plot of six fibroblast subpopulations in HC and PD samples. (**B**) Dot plot showing marker genes in fibroblast subpopulation. The color intensity represents the average expression level of marker genes, while the size of the dots reflects the percentage of cells expressing marker genes within each subtype. (**C**) Stacked chart of the proportions of six fibroblast subpopulations within the PD and HC groups. (**D**) Violin plot showing the expression level of OAT in HC (light blue) and PD (dark blue) samples. $^{***}P<0.001$. (**E-I**) Dot plot illustrating OAT expression across six fibroblast subtypes, pseudotime trajectory analysis showing fibroblasts subpopulations based on CytoTRACE and monocle2, and the dynamic trend of OAT expression along pseudotime. The cells are colored according to cell type or disease status and pseudotime value.

Inferring Intercellular Interactions

To investigate cellular interactions involving OAT + fibroblasts within the inflammatory microenvironment, we analyzed inferred interactions using Secreted Signaling databases. As illustrated in Fig. 7A, inferred interactions were significantly higher in the PD group (895) compared to the HC group (729), with elevated interaction strength in PD (0.154 vs. 0.053). Compared to HC, OAT + fibroblasts in the PD group exhibited more extensive and frequent communication with other cells, establishing them as central contributors to information flow (Fig. 7B) and as primary signal senders in both PD and HC (Fig. 7C). Moreover, we accessed the frequency of ligand-receptor communication between fibroblasts and other cell types in PD. We identified PD-specific intercellular communication pathways (Fig. 8A) and highlighted WNT, NRG, FASLG, and CHEMERIN as distinct signaling routes enriched in the PD group (Fig. 8B).

To determine dominant senders, receivers, mediators, and influencers in all inferred communication networks, we computed network centrality scores. The results revealed that OAT + fibroblasts, as primary signal senders, influence endothelial cells via the WNT pathway, potentially regulating angiogenesis or tissue repair. They also impact plasmacytoid dendritic cells (pDCs) through the CHEMERIN

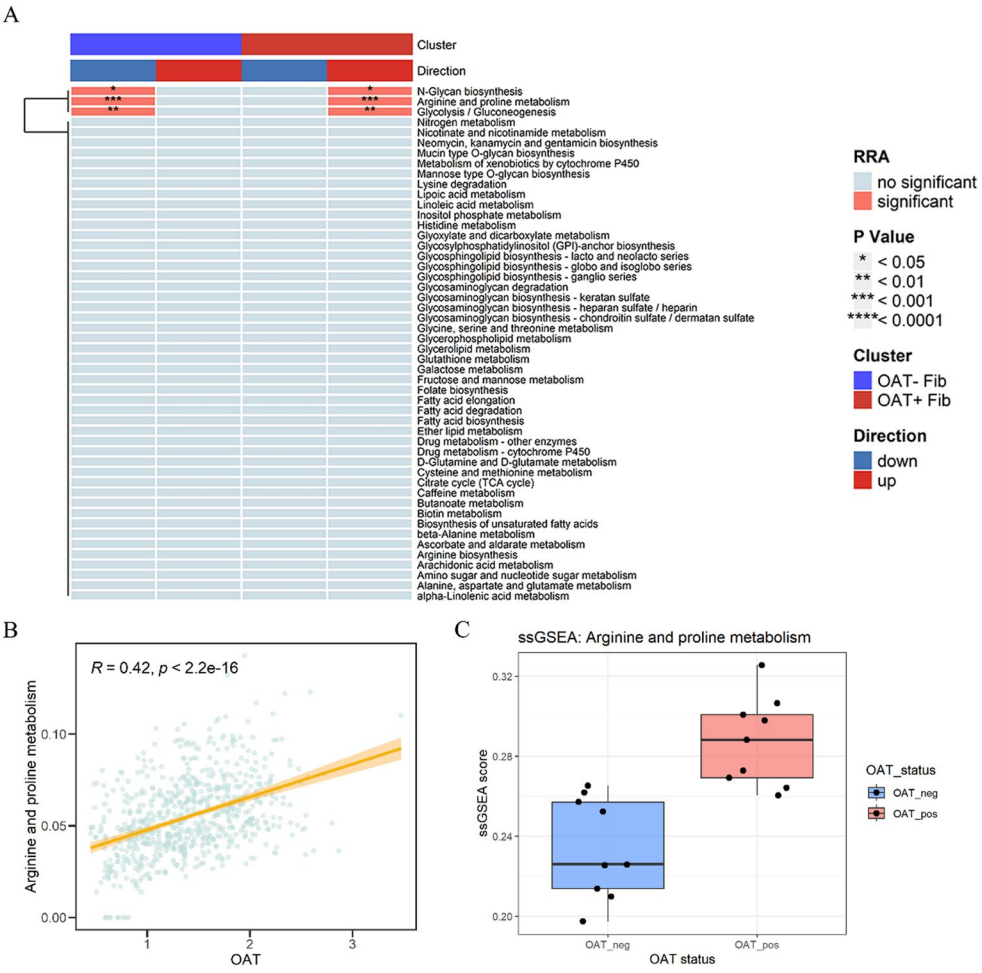

Fig. 6 Differential metabolic pathway enrichment in OAT+and OAT- fibroblasts. (**A**-**B**) Heatmaps of significantly enriched metabolic pathways in OAT+ (red) and OAT- (blue) fibroblast subpopulations, with directionality represented by red (upregulated) and blue (downregulated) colors. Analysis was based on KEGG and REACTOME databases. Pathways with statistical significance are marked, $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$; $^{****}P<0.0001$. (B) Correlation analyses between OAT expression and Arginine and Proline Metabolism pathway in fibroblasts. Scatter plots illustrate representative correlation patterns, with R values and p-values shown, indicating the strength and significance of the association between OAT expression levels and pathway activity. (**C**) ssGSEA algorithm supported the enrichment trend of the Arginine and proline metabolism pathway discovered by irGSEA.

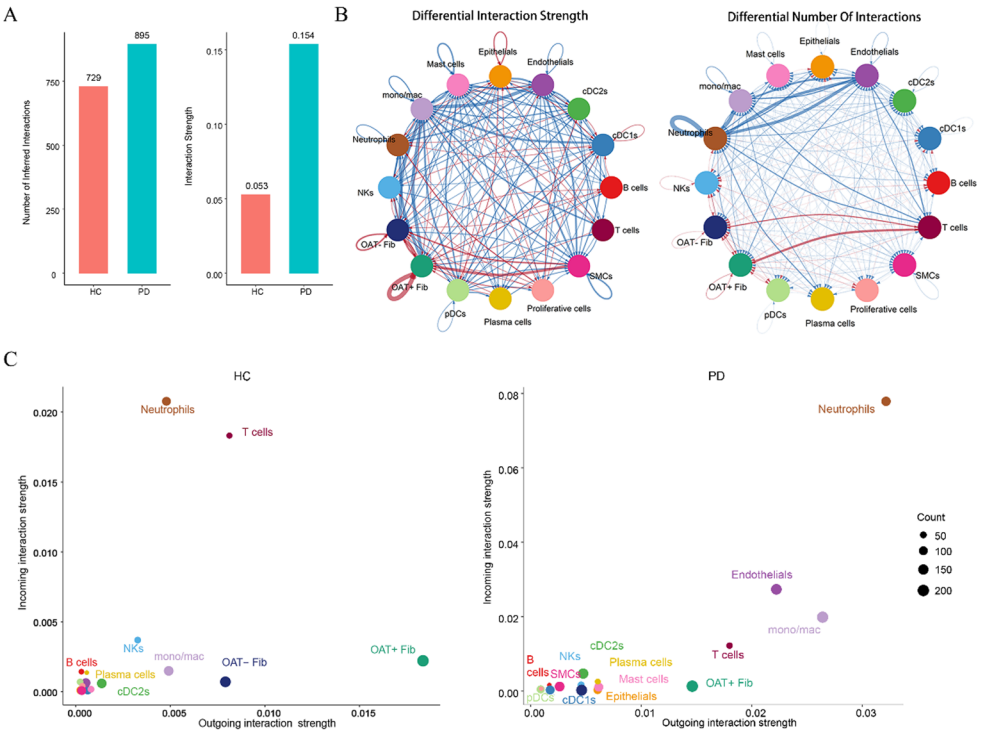

Fig. 7 Comparison of intercellular communication among various cell types in HC and PD. (**A**) Bar graphs showing the quantity and strength of cell communications in HC and PD groups. (**B**) Chord diagrams of the quantity and strength of cell communication among different cell types in the PD and HC groups. (**C**) Scatter plot representing the relative communication strength of each cell type within each group.

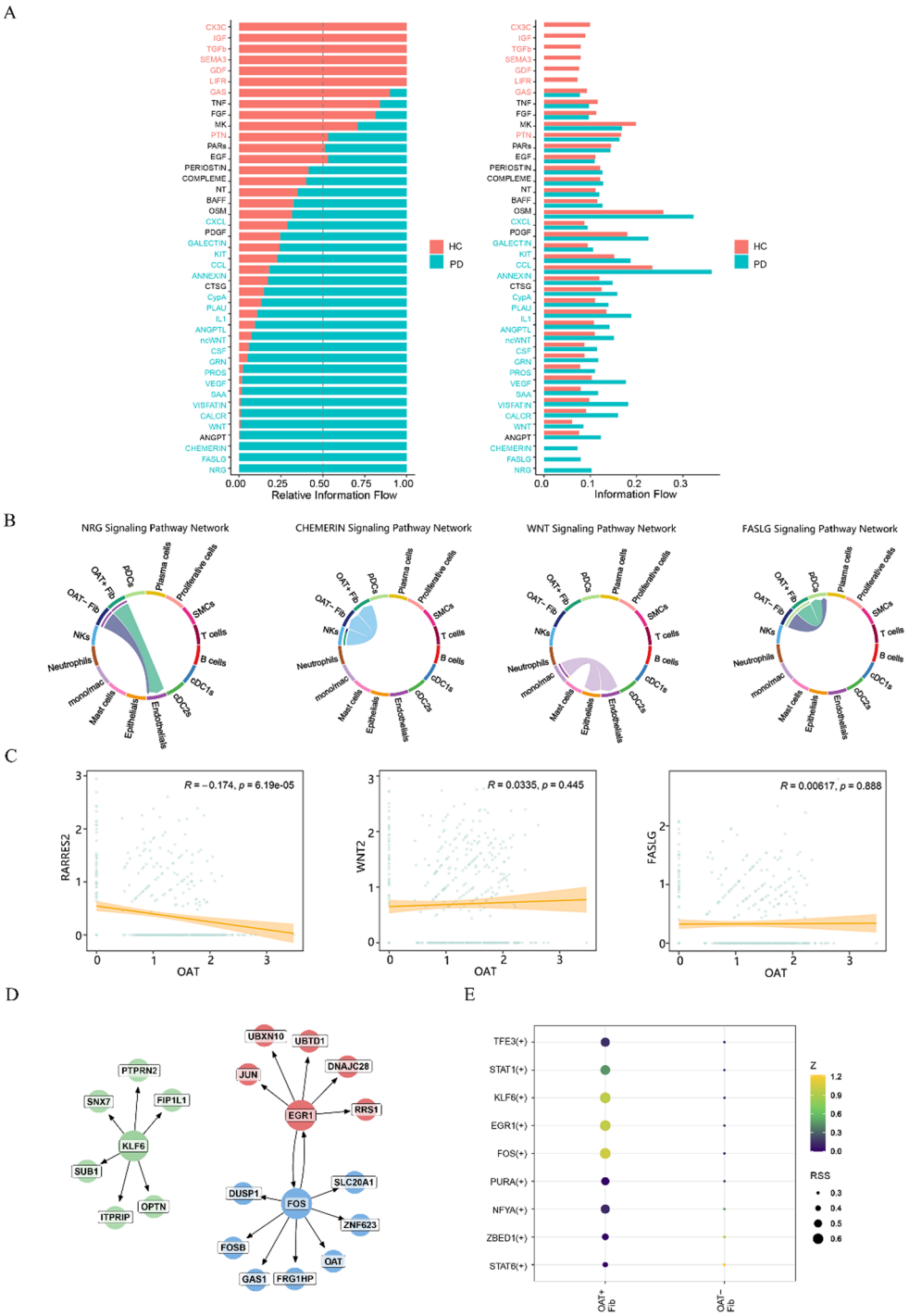

Fig. 8 (**A**) The overall signaling patterns within various cell types and comparative profiles of unique cell communication pathways in PD and HC groups. (**B**) Chord diagrams of specific pathway networks exclusive to PD, highlighting the WNT, NRG, FASLG, and CHEMERIN pathways, with arrows indicating communication direction. (**C**) Correlation analysis showing the association between OAT expression and the ligand RARRES2 in the CHEMERIN pathway. (**D**)Transcription factors between the OAT+Fib and OAT-Fib subgroups. (E)Transcription factor regulatory network. Z-score: standardized activity score of each regulon, reflecting its relative activation level in each cell type. RSS (Regulon Specificity Score): quantifies the cell-type specificity of each regulon; higher values indicate greater specificity.

pathway, highlighting a role in immune response modulation. Both OAT+and OAT- fibroblasts, as signal receivers, received FASLG signals from NK cells, suggesting that NK cells may regulate fibroblast survival or activation through the FASLG pathway to control inflammation (Fig. S4).

We further explored the expression of signaling molecules associated with these pathways. OAT+fibroblasts specifically exhibited high expression of the WNT2 ligand, RARRES2 ligand, and FASLG receptor (Fig. 8C). Finally, we examined the correlation between OAT and key signaling molecules in PD patients. Results indicated a weak negative correlation with RARRES2 (CHEMERIN pathway; R = -0.174, p=6.19e-05), with no significant correlation observed for WNT2 or FASLG (Fig. S5).

In this study, we utilized the pySCENIC analysis to identify upstream transcription factors associated with the expression of the OAT gene in fibroblasts from periodontitis patients. By comparing transcription factor activity between

Table 1 Candidate drug predicted by DSigDB.

Term	*P*-value	Adjusted *P*-value	Odds Ratio	Combined Score	Genes
Probenecid BOSS	0.0022	0.0193	951.29	5821.72	OAT
Sitagliptin BOSS	0.0024	0.0193	868.48	5239.42	DPP8
L-proline BOSS	0.0183	0.0496	108.28	433.11	OAT
D-Arginine BOSS	0.0186	0.0496	106.52	424.35	OAT

Table 2 Molecular Docking results of predicted drugs and proteins.

Target	PDB ID	Drug	PubChem ID	Binding energy (kcal/mol)
DPP8	7SVO	Sitagliptin	4,369,359	-9.4
OAT	1VZ7	Probenecid	4911	-6
OAT	1VZ7	L-proline	145,742	-5
OAT	1VZ7	D-Arginine	71,070	-5.9

the OAT + Fib and OAT- Fib subgroups, we found that FOS, KLF6, and EGR1 exhibited significantly higher regulatory activity in the OAT + Fib subgroup (Fig. 8D). Further prediction analysis of transcription factor-regulated genes indicated that FOS is likely a key upstream regulator of OAT (Fig. 8E).

Candidate Drug Prediction

DSigDB was used to predict potentially effective pharmacological agents, identifying candidates based on adjusted *p*-values (Table 1). The results showed that Probenecid, L-proline, and D-Arginine were associated with OAT, while Sitagliptin was linked to DPP8.

Molecular Docking

Molecular docking was performed to assess the binding affinity between candidate drugs and their corresponding target proteins. A total of four effective docking interactions were identified (Fig. 9A-D). Among them, DPP8 showed the strongest binding affinity with sitagliptin, with a docking energy of −9.4 kcal/mol, suggesting a stable and specific interaction. Full docking scores are summarized in Table 2.

Discussion

Periodontitis exhibits familial aggregation, suggesting a potential genetic predisposition. However, studies focusing on genetically susceptible forms of periodontitis remain limited, and the development of effective pharmacological therapies is still a challenge. In this study, we employed a combination of bioinformatics approaches to investigate druggable gene candidates associated with periodontitis. Our analysis revealed a putative causal relationship between OAT and DPP8 and the disease. Leveraging single-cell RNA sequencing, we further characterized the cell type–specific expression patterns of OAT and examined its potential functional roles in the pathogenesis of periodontitis.

Through unsupervised clustering, we identified distinct fibroblast subpopulations and found that OAT was predominantly expressed in fibroblasts. These OAT + fibroblasts exhibited dynamic roles in inflammation, ECM remodeling,

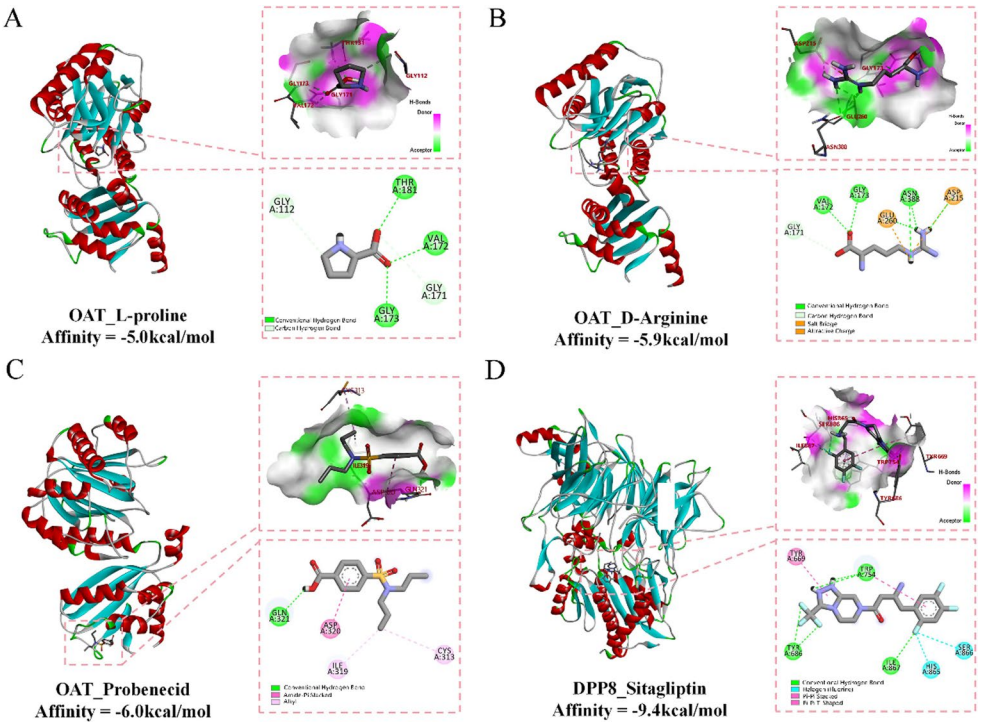

Fig. 9 Molecular docking results of predicted drugs and proteins. (**A**) OAT docking L-Proline. (**B**) OAT docking D-Arginine. (**C**) OAT docking Probenecid. (**D**) DPP8 docking Sitagliptin.

and cell–cell communication. Additionally, upstream regulatory analysis indicated FOS as a potential transcriptional regulator of OAT. Taken together, these results cautiously highlight the therapeutic potential of OAT in modulating disease progression.

A growing body of research has emphasized the role of fibroblasts in the regulation of inflammatory responses and tissue remodeling in periodontitis [53–55]. These cells are central to ECM organization and are essential for maintaining periodontal tissue integrity. Interestingly, fibroblasts showed significant enrichment in EXTRACELLULAR_MATRIX_ORGANIZATION, DEGRADATION_OF_THE_EXTRACELLULAR_MATRIX and SIGNALING_BY_MET, highlighting their role in ECM remodeling and adaptive tissue responses under inflammatory conditions. Notably, our data revealed that OAT expression was upregulated in fibroblasts derived from periodontitis samples, suggesting its involvement in ECM remodeling. Fibroblast subset proportions differed between healthy controls and periodontitis patients, with an increased prevalence of Fib1, Fib4, Fib5, and Fib6 in diseased tissues, indicative of a fibroblast-driven adaptation to the inflammatory and metabolic microenvironment. Pseudotime trajectory analysis revealed that OAT expression increased at later differentiation stages of inflammation-associated subsets (e.g., Fib1), implying a role in fibroblast-driven remodeling and inflammatory response during disease development. Consequently, OAT may have a critical role in modulating fibroblast-driven inflammation, contributing to tissue remodeling and immune response regulation in the pathogenesis of periodontitis.

As a chronic inflammatory disease, periodontitis is characterized by complex metabolic alterations influenced by proinflammatory cytokines (e.g., IL-1β, TNF-α) and microbial metabolites, which disrupt ornithine and proline metabolism—key pathways involved in collagen synthesis and degradation. To investigate the role of OAT in periodontitis-associated metabolic alterations, we investigated the metabolic profile of OAT + versus OAT − fibroblasts. Our results demonstrated significant enrichment of inflammation- and stress-related pathways, including arginine and proline metabolism. Importantly, OAT expression positively correlated with these pathways (e.g., arginine and proline metabolism: $R = 0.42$, $p < 2.2e\text{-}16$), suggesting a possible role for OAT as a mediator of metabolic adaptation, potentially enhancing fibroblast survival and function within the inflammatory microenvironment.

Cell–cell communication analysis further underscored the role of OAT + fibroblasts as central signaling hubs. These cells exhibited elevated interaction intensity (0.154 vs. 0.053 in controls) and greater ligand–receptor engagement, particularly through WNT, CHEMERIN, NRG, and FASLG signaling axes. For example, their interaction with endothelial cells via the WNT pathway may affect angiogenesis, while communication with plasmacytoid dendritic cells via CHEMERIN suggests a role in immune modulation. These findings position OAT + fibroblasts as critical orchestrators of inflammatory signaling, further supporting their relevance as therapeutic targets.

Regulatory network inference using pySCENIC suggested that FOS, a component of the AP-1 transcription factor complex, may act as an upstream modulator of OAT. FOS has been widely implicated in inflammation, tissue repair, and cellular stress responses [55, 56]. Its elevated activity in OAT + fibroblasts indicate a potential role in OAT-associated inflammatory and metabolic processes, consistent with previous reports linking FOS to cytokine production and ECM remodeling [57, 58].

Moreover, we observed upregulation of DPP8 in endothelial cells, implicating its potential involvement in vascular responses such as angiogenesis or endothelial dysfunction, which are commonly observed in chronic inflammatory states like periodontitis. However, given its low expression level, no further investigation was conducted.

DPP8 inhibitors like 1G244 can induce programmed cell death in hematologic malignancies [59]. To enhance efficacy and selectivity, a more DPP8-specific analog, tominostat, has been developed [60]. However, these inhibitors still show cytotoxicity and off-target inflammatory responses in animal models, which may limit their clinical use. While no OAT inhibitors have yet reached clinical approval, ongoing research has highlighted its high structural similarity to GABA-AT and its emerging potential as a therapeutic target in metabolic disorders and cancer [61]. From a translational perspective, the metabolic regulatory function of OAT suggests promise for clinical development.

This study applied a range of bioinformatics strategies to preliminarily characterize OAT and DPP8 in the setting of periodontitis. Recent integrative studies have combined GWAS with single-cell RNA-Seq to uncover cell-type-specific mechanisms in periodontitis. For example, Shi et al. identified dendritic cell-specific causal genes [62]. Chen et al. identified 14 genes (e.g., S100A8, S100A9) enriched in monocytes and B cells using integrative analysis, highlighting inflammation-related immune cell pathways as key drivers [63]. In contrast, our study focuses on fibroblast-associated genetic risk, identifying OAT + fibroblasts as critical regulators of metabolic rewiring and intercellular signaling in periodontal pathology, thereby expanding the cellular landscape of disease-associated targets beyond immune compartments.

The findings offer a starting point, though certain limitations remain. One key limitation is that the use of blood-derived cis-eQTLs may not fully capture regulatory mechanisms in fibroblasts or other oral cell types directly

implicated in periodontitis, due to known cell-type specificity in eQTL effects. Future studies incorporating cis-eQTL data from fibroblasts or gingival tissue will be important to improve inference accuracy. In addition, we acknowledge that single-cell RNA-Seq data are subject to dropout, which may lead to underestimation of low-level OAT expression. Although our binary classification captures robust patterns of functional heterogeneity, future validation using alternative methods (e.g., smFISH, flow cytometry) would further strengthen these findings. Although the Fib6 subpopulation exhibited distinct transcriptional features and high inferred stemness, its relatively small size warrants cautious interpretation of related findings, and future studies with larger sample sizes are needed to validate its role. The suggested regulatory link between FOS and OAT is still speculative and awaits experimental confirmation. Despite the quality of the single-cell transcriptomic data, they may not fully reflect the diversity of periodontal tissues across patient populations. Broader studies with larger cohorts, along with proteomic or metabolomic integration, are needed to clarify the metabolic role of OAT. Functional assays, such as gene knockout or chemical inhibition in OAT + fibroblasts, will help assess its therapeutic relevance. The potential contribution of DPP8 to endothelial inflammation also merits deeper investigation.

Conclusion

In this study, we identified OAT and DPP8 as potential therapeutic targets for periodontitis. Further experimental investigations are essential to validate these findings and to facilitate their translation into clinically applicable strategies for the management of periodontitis.

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Data Availability The original contributions delineated in the study are encapsulated within the article/Supplementary Material, and all the data used in this study are available in the public repository. Further inquiries may be directed to the corresponding author.

Declarations

Ethical Approval This study was based on publicly available anonymized genomewide association study summary statistics, and thus exempt from ethical compliance.

Competing interests The authors declare no competing interests.

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