Review Article

Salivary biomarker profile in rheumatoid arthritis and its interlinkage in oral manifestations: A comprehensive review

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Abstract

This study, a collaborative effort that delves into the interlinkage of salivary biomarkers in rheumatoid arthritis (RA), combines literature review with STRING and Cytoscape data. The discovery of elevated matrix metalloproteinases (MMPs) and pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-17 in saliva, and their link to joint and oral tissue damage in RA, is a significant finding. These biomarkers are crucial in understanding RA's inflammatory and destructive processes and oral manifestations. The analysis revealed significant interactions among biomarkers, with IL1B demonstrating strong coexpression with MMP1 and TIMP1, while MMP1 and TIMP1 showed a robust relationship. Cytoscape data further highlighted vital interactions, such as the solid functional relationship between IL2RB and IL2RG and the central role of MMP1 in matrix remodelling. The integration of these data, a result of our collective efforts, provides profound insights into the pathogenesis of RA and its impact on oral health, supporting the development of targeted diagnostic and therapeutic approaches.

Keywords: Oral manifestations, rheumatoid arthritis, salivary biomarkers

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease primarily characterized by synovitis and progressive joint degeneration.[1] Beyond its impact on joints, RA often manifests in the oral cavity, presenting as periodontal disease, oral hyposalivation, dysphagia, xerostomia, and temporomandibular joint abnormalities.[2] The hallmark of RA is synovial inflammation, which results from leukocyte infiltration and subsequent hyperplasia of the synovial membrane.[3] This inflammatory process increases fluid accumulation within the synovium, causing a hypoxic environment and reduced synovial capillary flow.[4]

Recent studies have revealed a significant correlation between RA and periodontitis, suggesting that elevated cytokine levels associated with RA, or increased titers of serum rheumatic factor, contribute to the development of periodontal disease.[5–7] Pathogens such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* play a

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critical role by inducing protein citrullination through their deaminase activity, which can stimulate the production of anti-citrullinated protein antibodies in RA patients.[8,9]

To understand the full impact of RA on oral health, it is crucial to explore the relationship between RA and periodontal disease, as well as to investigate salivary biomarkers related to periodontal health, including specific bacterial profiles and inflammatory mediators.[10] The oral symptoms associated with RA can significantly affect a patient's quality of life.[2] Salivary biomarkers have been proposed as potential indicators of oral involvement in RA.[10] Therefore, the objective of this review is to provide a comprehensive analysis of the pathophysiology of RA, its oral manifestations, and the intricate interactions between salivary biomarkers.

Interlinkage of salivary biomarkers in RA

Our investigation into salivary biomarkers in RA involved a comprehensive analysis of previously studied data from the literature, supplemented by new insights generated from STRING and Cytoscape analyses. This approach provided a deeper understanding of the interactions between these biomarkers and their implications for RA and its oral manifestations.

Matrix metalloproteinases (MMPs) and cytokines

Elevated levels of matrix metalloproteinases (MMPs) in saliva have been linked to oral and joint injury in RA due to their critical role in tissue remodelling and destruction.[11] Additionally, analysis of salivary pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17) helps elucidate their involvement in the inflammatory processes associated with RA-related oral symptoms.[10,12] These cytokines are integral to the inflammatory response seen in both RA and periodontitis.

Autoantibodies: Autoantibodies, including anti-cyclic citrullinated peptide (ABCA) and rheumatoid factor (RF), are commonly associated with RA. Their presence in saliva serves as a potential marker of systemic inflammation and oral involvement.[13] By examining these autoantibodies, we gain insights into how RA affects oral health.

Protein interactions and coexpression analysis

To explore the interactions among these biomarkers, we analyzed data using STRING and Cytoscape tools, as detailed in Figures 1 and 2, and summarized in Table 1. This analysis highlighted various coexpression values and combined scores, revealing significant interactions among

Table 1: Shows the coexpression status of salivary biomarkers based on string data analysis

Node1	Node2	Coexpression	Combined score
ABCA1	IL1B	0.072	0.612
IL1B	TIMP1	0.164	0.791
IL1B	MMP8	0.153	0.715
IL1B	TSLP	0.076	0.68
IL1B	MMP1	0.174	0.873
MMP1	TIMP1	0.123	0.999
MMP8	TIMP1	0.057	0.835

inflammatory markers. For instance, IL1B demonstrates strong interactions with MMP1 (coexpression: 0.174, combined score: 0.873) and TIMP1 (coexpression: 0.164, combined score: 0.791), indicating their roles in inflammation and matrix degradation. MMP1 and TIMP1 also show a robust functional relationship (combined score: 0.999), underscoring their importance in maintaining matrix balance.

By integrating data from existing literature with our STRING (string db.org) and Cytoscape analyses (cytoscape software), we have elucidated key interactions among salivary biomarkers relevant to RA. Elevated coexpression and combined scores among these biomarkers highlight their significant contributions to the inflammatory and destructive processes in RA and periodontitis [Table 2]. This comprehensive understanding enhances our insight into the pathogenesis of RA and its impact on oral health, paving the way for targeted diagnostic and therapeutic strategies.

Cytoscape analysis

The Cytoscape data provides a detailed view of interactions between various salivary biomarkers and their significance in RA. This analysis is based on three key metrics: coexpression, automated text mining, and a combined score that integrates these results to assess the overall importance of these interactions.

One notable finding is the strong interaction between Interleukin 2 Receptor Subunit Beta (IL2RB) and Interleukin 2 Receptor Subunit Gamma (IL2RG), which has the highest combined score of 0.999. This interaction is supported by high coexpression (0.266) and text mining results (0.998), indicating a robust and essential functional relationship. Similarly, the interaction between IL2RB and Janus Kinase 3 (JAK3) also shows a high combined score of 0.98, with moderate coexpression (0.155), suggesting a significant role in signalling pathways. Additionally, the IL2RB-Interleukin 7 Receptor (IL7R) interaction, with a combined score of 0.891, highlights its importance due to high coexpression (0.292) and substantial text mining support (0.853).

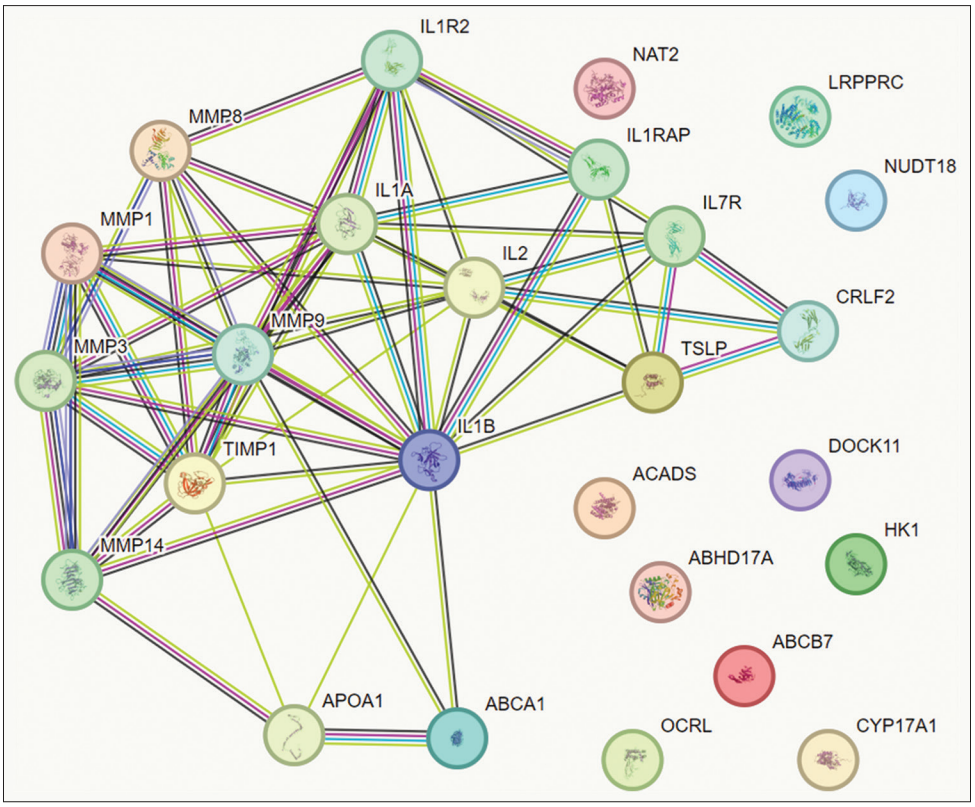

Figure 1: Shows string data of interlinkage of salivary biomarkers in association with RA and its oral manifestation (generated using the software https://string-db.org/)

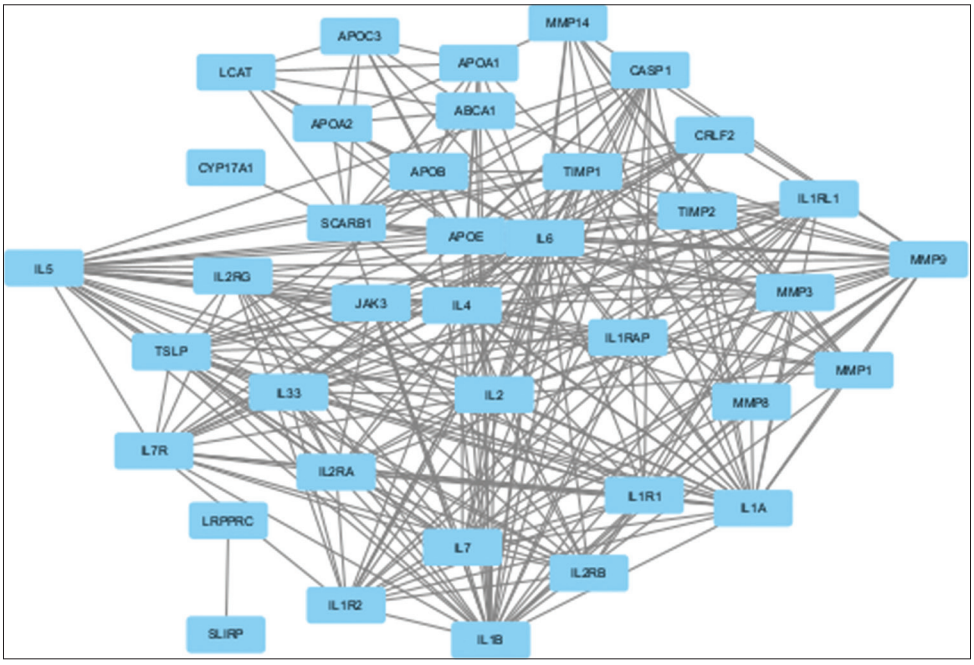

Figure 2: Shows the Cytoscape interlinkage of possible salivary biomarkers and their interlinkage in the pathogenesis of oral manifestations in RA (generated using Cytoscape software)

Matrix Metalloproteinase 1 (MMP1) shows strong interactions with other biomarkers, reflecting its central role in matrix remodelling. The interaction between MMP1 and MMP9 has a very high combined score of 0.974, supported by moderate coexpression (0.154). This suggests a significant role in matrix degradation processes. Additionally, the interaction between MMP1 and Tissue Inhibitor of Metalloproteinases 1 (TIMP1) also stands

Table 2: Cytoscape interlinkage of salivary biomarkers in association with RA and oral manifestations

Linkages of salivary biomarkers	Coexpression	Automated_textmining	Combined_score
IL2RB (interacts with) IL2RG	0.266	0.998	0.999
IL2RB (interacts with) JAK3	0.155	0.714	0.98
IL2RB (interacts with) IL7	0.104	0.829	0.941
IL2RB (interacts with) IL4	0.06	0.767	0.916
IL2RB (interacts with) IL7R	0.292	0.853	0.891
IL2RB (interacts with) IL6	0.056	0.608	0.859
IL2RB (interacts with) IL5	0	0.377	0.772
IL2RB (interacts with) TSLP	0	0.37	0.77
MMP1 (interacts with) MMP9	0.154	0.725	0.974
MMP1 (interacts with) MMP14	0.274	0.469	0.623
MMP1 (interacts with) MMP3	0.657	0.597	0.985
MMP1 (interacts with) TIMP2	0.095	0.921	0.936
MMP1 (interacts with) TIMP1	0.123	0.984	0.999
IL2RA (interacts with) JAK3	0.159	0.957	0.996
IL2RA (interacts with) IL6	0.074	0.869	0.953
IL2RA (interacts with) IL33	0.048	0.632	0.635
IL2RA (interacts with) IL2RG	0.172	0.997	0.999
IL2RA (interacts with) MMP9	0.075	0.467	0.486
IL2RA (interacts with) TSLP	0	0.399	0.78
IL2RA (interacts with) IL7R	0.122	0.906	0.914
IL2RA (interacts with) IL7	0.056	0.924	0.972
IL2RA (interacts with) IL5	0.061	0.754	0.912
IL2RA (interacts with) IL4	0.074	0.957	0.984
IL2RA (interacts with) IL2RB	0.148	0.995	0.999
IL2RG (interacts with) JAK3	0.226	0.998	0.999
IL2RG (interacts with) IL6	0.083	0.518	0.832
IL2RG (interacts with) TSLP	0	0.685	0.885
IL2RG (interacts with) IL7R	0.187	0.998	0.999
IL2RG (interacts with) IL7	0.089	0.997	0.999
IL2RG (interacts with) IL5	0	0.587	0.849
IL2RG (interacts with) IL4	0	0.996	0.999
MMP8 (interacts with) TIMP2	0.063	0.831	0.86
MMP8 (interacts with) MMP9	0.168	0.548	0.608
MMP8 (interacts with) TIMP1	0.057	0.809	0.835
IL1RL1 (interacts with) IL33	0.086	0.999	0.999
IL1RL1 (interacts with) TSLP	0.086	0.823	0.831
IL1RL1 (interacts with) IL7R	0.049	0.725	0.727
IL1RL1 (interacts with) IL6	0.057	0.681	0.686
IL1RL1 (interacts with) IL2RA	0.068	0.443	0.459
IL1RL1 (interacts with) IL7	0.086	0.422	0.449
IL1RL1 (interacts with) IL5	0.067	0.788	0.793
IL1RL1 (interacts with) IL4	0.074	0.594	0.608
IL1RL1 (interacts with) IL2	0.061	0.447	0.459
IL1RL1 (interacts with) IL2RB	0.042	0.403	0.404
IL1R1 (interacts with) IL6	0.086	0.997	0.997
IL1R1 (interacts with) IL33	0.129	0.988	0.99
IL1R1 (interacts with) IL2RA	0.049	0.758	0.76
IL1R1 (interacts with) IL2RG	0	0.544	0.544
IL1R1 (interacts with) MMP9	0.117	0.448	0.492
IL1R1 (interacts with) TSLP	0.068	0.405	0.422
IL1R1 (interacts with) IL1R2	0.192	0.971	0.997
IL1R1 (interacts with) IL1RAP	0.184	0.988	0.999
IL1R1 (interacts with) IL7R	0.067	0.682	0.69
IL1R1 (interacts with) MMP3	0.075	0.378	0.4
IL1R1 (interacts with) IL7	0.103	0.674	0.695
IL1R1 (interacts with) IL1RL1	0.105	0.928	0.938
IL1R1 (interacts with) IL5	0.078	0.796	0.803
IL1R1 (interacts with) IL4	0.07	0.798	0.804
IL1R1 (interacts with) IL2	0.069	0.742	0.749
IL1R1 (interacts with) IL2RB	0.042	0.558	0.558
IL33 (interacts with) IL6	0.068	0.793	0.798
IL33 (interacts with) MMP9	0.044	0.483	0.485
IL33 (interacts with) TSLP	0.123	0.924	0.93
IL33 (interacts with) IL7R	0.063	0.613	0.621
IL33 (interacts with) IL7	0.123	0.664	0.693

Contd...

Table 2: Contd...

Linkages of salivary biomarkers	Coexpression	Automated_textmining	Combined_score
IL33 (interacts with) IL5	0.086	0.935	0.938
IL33 (interacts with) IL4	0.085	0.904	0.908
IL1R2 (interacts with) IL6	0.062	0.732	0.738
IL1R2 (interacts with) MMP9	0.213	0.367	0.508
IL1R2 (interacts with) IL2RG	0.092	0.478	0.505
IL1R2 (interacts with) IL2RA	0.08	0.417	0.49
IL1R2 (interacts with) IL33	0.048	0.452	0.456
IL1R2 (interacts with) IL1RAP	0.144	0.975	0.998
IL1R2 (interacts with) IL7R	0.078	0.444	0.466
IL1R2 (interacts with) MMP8	0.167	0.348	0.464
IL1R2 (interacts with) IL1RL1	0.138	0.355	0.42
IL1R2 (interacts with) IL4	0.044	0.464	0.466
IL1R2 (interacts with) IL2	0.052	0.597	0.602
IL1R2 (interacts with) TIMP1	0.069	0.447	0.465
IL1R2 (interacts with) IL2RB	0.073	0.551	0.566
IL1RAP (interacts with) IL33	0	0.996	0.999
IL7 (interacts with) IL7R	0.059	0.999	0.999
IL7 (interacts with) JAK3	0.086	0.994	0.997
IL7 (interacts with) TSLP	0.056	0.867	0.869
IL7 (interacts with) MMP9	0.088	0.4	0.429
MMP3 (interacts with) MMP9	0.145	0.514	0.956
MMP3 (interacts with) TIMP2	0.088	0.959	0.967
MMP3 (interacts with) SCARB1	0.068	0.546	0.558
MMP3 (interacts with) MMP8	0	0.458	0.472
MMP3 (interacts with) TIMP1	0.115	0.998	0.999
IL1A (interacts with) IL1R1	0.085	0.999	0.999
IL1A (interacts with) IL1B	0.961	0.983	0.999
IL1A (interacts with) IL1R2	0.087	0.996	0.999
IL1A (interacts with) IL1RAP	0.086	0.997	0.998
IL1A (interacts with) IL6	0.376	0.974	0.989
IL1A (interacts with) IL33	0.085	0.812	0.82
IL1A (interacts with) MMP3	0.08	0.797	0.807
IL1A (interacts with) MMP1	0.115	0.779	0.798
IL1A (interacts with) IL7	0.067	0.783	0.789
IL1A (interacts with) MMP9	0.08	0.72	0.734
IL1A (interacts with) IL7R	0.097	0.696	0.713
IL1A (interacts with) TSLP	0.131	0.608	0.645
IL1A (interacts with) IL2RA	0.117	0.582	0.615
IL1A (interacts with) IL2RG	0.064	0.551	0.561
IL1A (interacts with) MMP14	0.087	0.37	0.406
IL1A (interacts with) TIMP2	0.111	0.505	0.541
IL1A (interacts with) SCARB1	0.054	0.526	0.532
IL1A (interacts with) MMP8	0.055	0.521	0.532
IL1A (interacts with) IL1RL1	0.064	0.847	0.852
IL1A (interacts with) IL5	0.134	0.909	0.918
IL1A (interacts with) IL4	0.111	0.992	0.995
IL1A (interacts with) IL2	0.111	0.997	0.997
IL1A (interacts with) TIMP1	0.111	0.647	0.672
IL5 (interacts with) IL7	0	0.995	0.995
IL5 (interacts with) IL6	0.042	0.977	0.977
IL5 (interacts with) IL7R	0	0.646	0.87
IL5 (interacts with) TSLP	0.105	0.859	0.868
IL5 (interacts with) JAK3	0	0.447	0.654
IL5 (interacts with) MMP1	0	0.547	0.547
IL5 (interacts with) MMP9	0	0.532	0.532
IL5 (interacts with) MMP3	0	0.531	0.531
IL5 (interacts with) TIMP1	0	0.445	0.445
IL4 (interacts with) IL7	0.086	0.998	0.998
IL4 (interacts with) JAK3	0	0.986	0.998
IL4 (interacts with) IL5	0.351	0.983	0.988
IL4 (interacts with) IL6	0.044	0.978	0.986
IL4 (interacts with) IL7R	0	0.87	0.952
IL4 (interacts with) TSLP	0.11	0.862	0.872
IL4 (interacts with) MMP9	0.052	0.684	0.687
IL4 (interacts with) MMP3	0.052	0.651	0.655

Contd...

Table 2: Contd...

Linkages of salivary biomarkers	Coexpression	Automated_textmining	Combined_score
IL4 (interacts with) SCARB1	0	0.571	0.571
IL4 (interacts with) MMP1	0.053	0.479	0.486
IL4 (interacts with) MMP8	0.052	0.403	0.41
IL4 (interacts with) TIMP1	0	0.72	0.72
IL2 (interacts with) IL5	0.266	0.999	0.999
IL2 (interacts with) JAK3	0.042	0.996	0.999
IL2 (interacts with) IL2RG	0.044	0.998	0.999
IL2 (interacts with) IL2RA	0.082	0.999	0.999
IL2 (interacts with) IL6	0.055	0.999	0.999
IL2 (interacts with) IL4	0.432	0.999	0.999
IL2 (interacts with) IL7	0.049	0.997	0.997
IL2 (interacts with) IL7R	0.042	0.942	0.978
IL2 (interacts with) IL33	0.043	0.825	0.825
IL2 (interacts with) TSLP	0.091	0.625	0.645
IL2 (interacts with) MMP9	0.053	0.596	0.601
IL2 (interacts with) MMP3	0.053	0.464	0.471
IL2 (interacts with) MMP1	0.055	0.432	0.441
IL2 (interacts with) TIMP1	0	0.487	0.487
IL2 (interacts with) IL2RB	0.047	0.997	0.999
IL7R (interacts with) TSLP	0	0.997	0.999
IL7R (interacts with) JAK3	0.128	0.919	0.988
MMP14 (interacts with) MMP9	0.092	0.822	0.831
MMP14 (interacts with) MMP3	0.187	0.2	0.537
MMP14 (interacts with) TIMP2	0.123	0.999	0.999
MMP14 (interacts with) TIMP1	0.172	0.996	0.999
TIMP1 (interacts with) TIMP2	0.147	0.521	0.582
IL6 (interacts with) JAK3	0.067	0.757	0.914
IL6 (interacts with) MMP9	0.106	0.93	0.959
IL6 (interacts with) TSLP	0.074	0.665	0.677
IL6 (interacts with) MMP1	0.169	0.731	0.854
IL6 (interacts with) MMP14	0.124	0.489	0.533
IL6 (interacts with) IL7R	0.109	0.753	0.916
IL6 (interacts with) MMP3	0.16	0.795	0.887
IL6 (interacts with) IL7	0.067	0.983	0.983
IL6 (interacts with) TIMP2	0.086	0.789	0.799
IL6 (interacts with) SCARB1	0.075	0.7	0.71
IL6 (interacts with) MMP8	0.086	0.635	0.653
IL6 (interacts with) TIMP1	0.152	0.888	0.938
MMP9 (interacts with) TIMP2	0.133	0.997	0.998
MMP9 (interacts with) SCARB1	0.062	0.547	0.557
MMP9 (interacts with) TIMP1	0.075	0.999	0.999
IL1B (interacts with) IL1RAP	0.062	0.997	0.999
IL1B (interacts with) IL1R1	0.087	0.999	0.999
IL1B (interacts with) IL1R2	0.179	0.996	0.999
IL1B (interacts with) IL6	0.515	0.989	0.996
IL1B (interacts with) MMP9	0.275	0.932	0.949
IL1B (interacts with) IL7	0.083	0.905	0.909
IL1B (interacts with) IL33	0.078	0.886	0.89
IL1B (interacts with) MMP1	0.174	0.849	0.873
IL1B (interacts with) IL2RA	0.157	0.851	0.869
IL1B (interacts with) MMP3	0.117	0.812	0.832
IL1B (interacts with) IL7R	0.195	0.712	0.758
IL1B (interacts with) TSLP	0.076	0.668	0.68
IL1B (interacts with) IL2RG	0.129	0.568	0.608
IL1B (interacts with) JAK3	0.111	0.488	0.526
IL1B (interacts with) MMP14	0.092	0.481	0.514
IL1B (interacts with) TIMP2	0.111	0.594	0.624
IL1B (interacts with) SCARB1	0.06	0.708	0.714
IL1B (interacts with) MMP8	0.153	0.667	0.715
IL1B (interacts with) IL1RL1	0.063	0.883	0.892
IL1B (interacts with) IL5	0.104	0.998	0.998
IL1B (interacts with) IL4	0.072	0.998	0.998
IL1B (interacts with) IL2	0.073	0.999	0.999
IL1B (interacts with) TIMP1	0.164	0.761	0.791
ABCA1 (interacts with) IL6	0.063	0.604	0.613
ABCA1 (interacts with) MMP9	0.088	0.43	0.458

Contd...

Table 2: Contd...

Linkages of salivary biomarkers	Coexpression	Automated_textmining	Combined_score
ABCA1 (interacts with) APOA2	0.059	0.872	0.874
ABCA1 (interacts with) LCAT	0.054	0.911	0.912
ABCA1 (interacts with) IL1B	0.072	0.599	0.612
ABCA1 (interacts with) SCARB1	0.064	0.932	0.934
ABCA1 (interacts with) APOE	0.084	0.979	0.98
ABCA1 (interacts with) APOA1	0.055	0.999	0.999
ABCA1 (interacts with) APOB	0.042	0.861	0.861
ABCA1 (interacts with) APOC3	0.042	0.744	0.744

out with the highest combined score of 0.999, indicating a crucial balance in matrix remodelling and inhibition.

Interleukin 2 Receptor Subunit Alpha (IL2RA) exhibits significant interactions, particularly with JAK3 and IL2RB. The IL2RA-JAK3 interaction has a high combined score of 0.996, with strong text mining support (0.957), underlining its importance in signalling pathways. Similarly, the IL2RA-IL2RB interaction, with a combined score of 0.999, reflects a critical role within the interleukin receptor complex.

Interleukin 6 (IL6) also plays a prominent role, with notable interactions such as IL6-MMP1 and IL6-MMP9. The interaction between IL6 and MMP1 has a high combined score of 0.854, indicating a significant involvement in inflammation and matrix degradation. The IL6-MMP9 interaction, with a combined score of 0.959 and moderate coexpression (0.106), further emphasizes its role in matrix remodelling.

Interleukin 1 Beta (IL1B) is another key player, with strong interactions with Interleukin 1 Receptor Type 1 (IL1R1) and MMP9. The IL1B-IL1R1 interaction shows a very high combined score of 0.999, reflecting its critical role in inflammatory responses. The interaction between IL1B and MMP9, with a combined score of 0.949, highlights its involvement in matrix degradation processes.

Lastly, ATP-Binding Cassette Transporter A1 (ABCA1) shows significant interaction with Apolipoprotein A1 (APOA1), with a very high combined score of 0.999. This suggests a strong functional relationship with important implications in lipid metabolism. Overall, the Cytoscape data reveals a complex network of salivary biomarkers involved in RA, emphasizing their roles in inflammation, matrix remodelling, and potential therapeutic targets.

Association between RA and periodontitis

RA and periodontitis are chronic inflammatory diseases that share common pathophysiological mechanisms. Both conditions involve an inflammatory response that can lead to tissue destruction. Recent studies have suggested a bidirectional relationship between RA and periodontitis, where each disease may influence the severity and progression of the other. Salivary biomarkers offer a non-invasive approach to studying this interconnection, providing insights into the inflammatory processes underlying both diseases.

RA is an autoimmune disease characterized by chronic inflammation of the synovial joints, leading to joint destruction and disability. It is driven by an aberrant immune response involving various pro-inflammatory cytokines and autoantibodies. Periodontitis, on the other hand, is a severe form of gum disease caused by bacterial infection. It results in the inflammation and destruction of the supporting structures of the teeth, including the periodontal ligament and alveolar bone.

Epidemiological studies have shown a higher prevalence of periodontitis in RA patients compared to the general population. For example, a meta-analysis indicated that individuals with RA are twice as likely to develop periodontitis. Conversely, patients with periodontitis are at a higher risk of developing RA. Both RA and periodontitis share common inflammatory pathways. Key cytokines, such as IL-1β, IL-6, and TNF-α, play pivotal roles in the pathogenesis of both diseases. Additionally, the presence of shared genetic risk factors, such as certain HLA-DR alleles, further supports the link between these conditions.

Salivary biomarkers provide a non-invasive means to study the inflammatory milieu in both RA and periodontitis. Significant biomarkers include cytokines like IL-1β, IL-6, and TNF-α, which are elevated in the saliva of patients with both RA and periodontitis. These cytokines are central to the inflammatory response and are involved in tissue destruction in both diseases. Enzymes such as MMPs, particularly MMP-8 and MMP-9, are increased in the saliva of RA and periodontitis patients. MMPs contribute to the breakdown of extracellular matrix components, facilitating tissue degradation. Additionally, autoantibodies like RF and anti-citrullinated protein antibodies (ACPAs) are commonly detected in the saliva of RA patients. These autoantibodies

have also been found in individuals with periodontitis, suggesting a potential link in autoimmunity.

To understand the interlinkage between RA, periodontitis, and salivary biomarkers, STRING and Cytoscape data analysis were utilized. String data analysis predicts protein-protein interactions and functional associations between biomarkers. Our analysis revealed significant interactions between key inflammatory cytokines (IL-1β, IL-6, TNF-α) and MMPs in both RA and periodontitis, suggesting a shared inflammatory network driving both diseases. Cytoscape visualization illustrated the complex network of interactions between salivary biomarkers in RA and periodontitis. Central nodes in the network included IL-1β, IL-6, and TNF-α, indicating their critical role in the inflammatory processes. The visualization also highlighted clusters of biomarkers that are co-expressed in both conditions, reinforcing the bidirectional relationship.

Understanding the interlinkage between RA, periodontitis, and salivary biomarkers has several clinical implications. Salivary biomarkers can aid in the early diagnosis and monitoring of both RA and periodontitis, potentially leading to more timely and effective interventions. Given the bidirectional relationship, integrated management of RA and periodontitis is essential. Regular dental check-ups and periodontal care should be part of the standard care for RA patients. Identifying specific biomarker profiles can help tailor treatment strategies for patients with coexisting RA and periodontitis, improving overall outcomes.

Epidemiological evidence and shared pathophysiological mechanisms support the association between RA and periodontitis. Salivary biomarkers provide a valuable tool for studying this interconnection, offering insights into the inflammatory processes driving both diseases. Understanding these interlinkages can enhance diagnostic and therapeutic approaches, ultimately improving patient care.

Salivary biomarkers and periodontal pathogens in RA

Salivary biomarkers have become increasingly significant in understanding the connection between RA and its oral manifestations, particularly those associated with periodontal pathogens such as *A. actinomycetemcomitans* and *P. gingivalis*.[14-16] Elevated levels of citrullinated proteins and ACPAs in saliva reflect the autoimmune processes underlying RA, with these biomarkers being linked to the activity of periodontal pathogens.[17-19] These pathogens induce citrullination in neutrophils, leading to the release of citrullinated autoantigens that are detectable in saliva.[20-23] Although RA patients have higher levels of specific salivary biomarkers, the composition of subgingival plaque microbiota does not always align with disease severity, suggesting a complex interplay between salivary biomarkers and microbial profiles.[23-26] Integrating salivary biomarker analysis with advanced methodologies, such as STING pathway assessments and Cytoscape network analyses, offers new insights into RA's pathophysiology and its association with periodontal disease. This approach may enhance diagnostic accuracy and inform therapeutic strategies, potentially improving outcomes through targeted periodontal and RA treatments.

Salivary biomarkers linkage in periodontal biofilm alteration

The "two-hit" concept of RA describes the development of the disease through a sequence of events. Initially, the first "hit" involves a breakdown in immune tolerance to specific citrullinated peptides, which can trigger gingivitis. The second "hit" involves epitope spreading, where the immune response extends to additional citrullinated host proteins, ultimately leading to arthritis.[27,28] A key player in this process is *P. gingivalis*, which produces peptidyl arginine deiminase (PAD), an enzyme that modifies arginine residues in proteins to citrulline. This modification occurs in proteins such as collagen type II, fibrin, fibrinogen, vimentin, and α-enolase, resulting in the formation of anti-citrulline antibodies.[29]

Salivary biomarkers are crucial in understanding the interlinkage between periodontal disease and RA. Specifically, peptidylarginine deiminases PAD-2 and PAD-4, which are expressed in varying levels in RA patients, are found in or near citrullinated fibrin deposits. The expression levels of these enzymes are likely associated with the degree of inflammation.[29] Moreover, the virulence factors of *P. gingivalis*, including hemagglutinins, fimbriae, lipopolysaccharide (LPS), and cysteine proteases (gingipains), contribute to chronic inflammation by inducing pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[29]

Elevated levels of citrullination, PAD-2, and PAD-4 have been observed in the saliva of periodontitis patients, even in the absence of specific periodontal pathogens like *P. gingivalis* and A. actinomycetemcomitans leukotoxins.[30] This finding highlights the potential of salivary biomarkers as indicators of both periodontal disease and RA. The presence of these biomarkers may suggest underlying inflammatory processes that warrant further investigation to elucidate their full role in RA pathogenesis.

Interlinkage of salivary biomarkers and gut microbiome in rheumatoid arthritis

The gut microbiome significantly influences the host

immune system and is implicated in developing RA through molecular mimicry, epitope spreading, pathogen persistence, and toll-like receptor stimulation. These interactions can also induce epigenetic modifications that impact gene function, including changes in DNA methylation, histone modifications, and micro-RNA expression.

Among the gut microbiota, *Prevotella copri* has been identified as a notable factor in RA development, with higher levels observed in RA patients compared to healthy controls.[2,31–34] This bacterium triggers immune responses that may contribute to RA onset and progression. Research by Scher *et al.* (2013)[33] highlighted increased *P. copri* levels in the stools of new-onset RA patients, with subsequent studies finding *P. copri* epitopes in the synovial tissue and circulation of RA patients.[24] The presence of these epitopes suggests a potential activation of Th1 and antibody responses in RA subgroups.[32]

The interlinkage between gut microbiome modulation and salivary biomarkers is particularly relevant. Elevated levels of salivary biomarkers such as citrullinated PADs have been associated with RA and its oral manifestations. These biomarkers, which include PADs and citrullinated peptides, can serve as indicators of ongoing inflammatory processes linked to both gut microbiome changes and oral health issues.

Recent findings indicate that increased levels of these biomarkers in saliva correlate with RA-related oral manifestations, such as periodontal disease and oral mucosal changes. This underscores the importance of salivary biomarker analysis in understanding RA pathology and monitoring disease progression.

Despite growing evidence, many aspects of the gut microbiome's role in RA and its impact on salivary biomarkers remain unclear. Further research is needed to fully elucidate these interactions and identify potential therapeutic targets for RA management through microbiome modulation and salivary biomarker profiling.[35]

Association of gingivitis in RA

Both the aetiology and epidemiology of RA are significantly associated with gingival disease.[36] Gingival disease, characterized by chronic inflammation and the destruction of supporting tissues around the teeth, is caused by oral microbial agents.[36] Both gingival disease and RA share similar inflammatory mechanisms and cytokine profiles,[37] suggesting a non-causal but notable relationship between the two conditions.[15] The oral pathogen *P. gingivalis*, known for its role in gingival disease, produces an enzyme that induces citrullination, a key process linked to RA.[14] This pathogen's citrullinated antigens in gingival tissue correlate with ACPAs and specific autoantibodies, such as those against human citrullinated α-enolase, which are involved in RA autoimmunity.[14,28]

The interplay between gingivitis and RA underscores the significant link between oral health and systemic inflammation.[38,39] Gingivitis, an inflammatory gum condition frequently observed in RA patients, may exacerbate disease progression through mechanisms involving salivary biomarkers. Elevated levels of biomarkers such as PADs and ACPAs in saliva are associated with both periodontal disease and RA. The presence of *P. gingivalis* in periodontal infections contributes to increased citrullination of host proteins, thereby amplifying systemic inflammation and RA symptoms. These salivary biomarkers reflect oral health status and serve as indicators of RA disease activity and severity, highlighting the importance of integrated strategies for managing gingivitis and monitoring RA progression.

CONCLUSION

RA is a multifaceted systemic condition that significantly impacts not only the joints but also various aspects of oral health. The interplay between salivary biomarkers and RA reveals crucial insights into the pathophysiology of the disease, particularly in relation to its oral manifestations. Elevated levels of specific salivary biomarkers, such as MMPs and pro-inflammatory cytokines, correlate strongly with both joint and oral tissue damage, providing valuable markers for monitoring disease progression and response to treatment. The intricate relationships among these biomarkers, as highlighted by our review, underscore the potential of salivary diagnostics in enhancing the management of RA and improving patient outcomes.

Future scope

Future research should focus on exploring the complex interactions among immunological responses, salivary biomarkers, the oral microbiota, and the overall pathophysiology of RA. This includes investigating how specific salivary biomarkers can be used to predict the onset of oral manifestations and assess disease severity. Advances in understanding these interactions could lead to the identification of novel therapeutic targets and the development of personalized treatment strategies tailored to individual patient profiles. Additionally, further studies should aim to elucidate the role of the oral microbiota in RA, as its interaction with salivary biomarkers could unveil new mechanisms of disease and potential avenues for intervention. Ultimately, integrating these insights will

facilitate more effective and targeted approaches to managing RA, enhancing both systemic and oral health outcomes.

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Conflicts of interest

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REFERENCES

1. Karataş E, Kul A, Camilleri J, Yonel Z. Association between rheumatoid arthritis and pulpal-periapical pathology: A systematic review. Clin Oral Investig 2023;27:7019-28.
2. Gualtierotti R, Marzano AV, Spadari F, Cugno M. Main oral manifestations in immune-mediated and inflammatory rheumatic diseases. J Clin Med 2018;8:21.
3. Morović-Vergles J. [Pathophysiology of rheumatoid arthritis]. Reumatizam 2003;50:15-7.
4. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A Synopsis. Am J Manag Care. 2014;20(7 Suppl):S128-35.
5. Detert J, Pischon N, Burmester GR, Buttgereit F. The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther 2010;12:218.
6. Araújo VMA, Melo IM, Lima V. Relationship between periodontitis and rheumatoid arthritis: Review of the literature. Mediators Inflamm 2015;2015:259074.
7. Varshney S, Sharma M, Kapoor S, Siddharth M. Association between rheumatoid arthritis and periodontitis in an adult population-A cross sectional study. J Clin Exp Dent 2021;13:e980-6.
8. Thé J, Ebersole JL. Rheumatoid factor (RF) distribution in periodontal disease. J Clin Immunol 1991;11:132-42.
9. McGraw WT, Potempa J, Farley D, Travis J. Purification, characterization, and sequence analysis of a potential virulence factor from Porphyromonas gingivalis, peptidylarginine deiminase. Infect Immun 1999;67:3248-56.
10. Mirrielees J, Crofford LJ, Lin Y, Kryscio RJ, Dawson DR 3rd, Ebersole JL, *et al*. Rheumatoid arthritis and salivary biomarkers of periodontal disease. J Clin Periodontol 2010;37:1068-74.
11. Äyräväinen L, Heikkinen AM, Kuuliala A, Ahola K, Koivuniemi R, Laasonen L, *et al*. Inflammatory biomarkers in saliva and serum of patients with rheumatoid arthritis with respect to periodontal status. Ann Med 2018;50:333-44.
12. Eriksson K, Lundmark A, Delgado LF, Hu YOO, Fei G, Lee L, *et al*. Salivary microbiota and host-inflammatory responses in periodontitis affected individuals with and without rheumatoid arthritis. Front Cell Infect Microbiol 2022;12:841139.
13. Tar I, Csősz É, Végh E, Lundberg K, Kharlamova N, Soós B, *et al*. Salivary citrullinated proteins in rheumatoid arthritis and associated periodontal disease. Sci Rep 2021;11:13525.
14. Sakkas LI, Bogdanos DP, Katsiari C, Platsoucas CD. Anti-citrullinated peptides as autoantigens in rheumatoid arthritis-relevance to treatment. Autoimmun Rev 2014;13:1114-20.
15. Zorba M, Melidou A, Patsatsi A, Ioannou E, Kolokotronis A. The possible role of oral microbiome in autoimmunity. Int J Womens Dermatol 2020;6:357-64.
16. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primer 2017;3:17038.
17. Fuggle NR, Smith TO, Kaul A, Sofat N. Hand to mouth: A systematic review and meta-analysis of the association between rheumatoid arthritis and periodontitis. Front Immunol 2016;7:80.
18. Konig MF, Abusleme L, Reinholdt J, Palmer RJ, Teles RP, Sampson K, *et al*. Aggregatibacter actinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Sci Transl Med 2016;8:369ra176. doi: 10.1126/scitranslmed.aaj1921.
19. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25:134-44.
20. Corrêa JD, Fernandes GR, Calderaro DC, Mendonça SMS, Silva JM, Albiero ML, *et al*. Oral microbial dysbiosis linked to worsened periodontal condition in rheumatoid arthritis patients. Sci Rep 2019;9:8379.
21. Lorenzo D, GianVincenzo Z, Carlo Luca R, Karan G, Jorge V, Roberto M, *et al*. Oral-Gut Microbiota and Arthritis: Is There an Evidence-Based Axis? J Clin Med 2019;8:0. [doi: 10.3390/jcm8101753].
22. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
23. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: Pathological mechanisms and modern pharmacologic therapies. Bone Res 2018;6:15.
24. Wilson TM, Trent B, Kuhn KA, Demoruelle MK. Microbial influences of mucosal immunity in rheumatoid arthritis. Curr Rheumatol Rep 2020;22:83.
25. de Pablo P, Chapple ILC, Buckley CD, Dietrich T. Periodontitis in systemic rheumatic diseases. Nat Rev Rheumatol 2009;5:218-24.
26. Mikuls TR, Payne JB, Yu F, Thiele GM, Reynolds RJ, Cannon GW, *et al*. Periodontitis and porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66:1090-100.
27. Samborska-Mazur J, Sikorska D, Wyganowska-Świątkowska M. The relationship between periodontal status and rheumatoid arthritis – Systematic review. Reumatologia 2020;58:236-42.
28. Engström M, Eriksson K, Lee L, Hermansson M, Johansson A, Nicholas AP, *et al*. Increased citrullination and expression of peptidylarginine deiminases independently of P. gingivalis and A. actinomycetemcomitans in gingival tissue of patients with periodontitis. J Transl Med 2018;16:214.
29. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, *et al*. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum 2010;62:2662-72. [doi: 10.1002/art.27552].
30. Foulquier C, Sebbag M, Clavel C, Chapuy-Regaud S, Al Badine R, Méchin MC, *et al*. Peptidyl arginine deiminase type 2 (PAD-2) and PAD-4 but not PAD-1, PAD-3, and PAD-6 are expressed in rheumatoid arthritis synovium in close association with tissue inflammation. Arthritis Rheum 2007;56:3541-53.
31. Maeda Y, Kurakawa T, Umemoto E, Motooka D, Ito Y, Gotoh K, *et al*. Dysbiosis contributes to arthritis development via activation of autoreactive T cells in the intestine. Arthritis Rheumatol 2016;68:2646-61.
32. Pianta A, Arvikar S, Strle K, Drouin EE, Wang Q, Costello CE, *et al*. Evidence of the immune relevance of prevotella copri, a gut microbe, in patients with rheumatoid arthritis. Arthritis Rheumatol 2017;69:964-75.
33. Scher JU, Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, *et al*. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. Elife 2013;2:e01202.
34. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D, *et al*. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med 2015;21:895-905.
35. Chen J, Wright K, Davis JM, Jeraldo P, Marietta EV, Murray J, *et al*. An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. Genome Med 2016;8:43.
36. Huang LG, Chen G, Chen DY, Chen HH. Factors associated with the risk of gingival disease in patients with rheumatoid arthritis. PLoS One 2017;12:e0186346.
37. Darrah E. Gum disease linked to rheumatoid arthritis. Johns Hopkins Rheumatology. Published January 23, 2017. Available from: https://www.hopkinsrheumatology.org/2017/01/gum-disease-linked-to-rheumatoid-arthritis/. [Last accessed on 2024 Jan 19].
38. Shiroky JB, Neville C, Esdaile JM, Choquette D, Zummer M, Hazeltine M, *et al*. Low-dose methotrexate with leucovorin (folinic acid) in the management of rheumatoid arthritis. Results of a multicenter randomized, double-blind, placebo-controlled trial. Arthritis Rheum 1993;36:795-803.
39. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: A systematic review of the literature. Ann Rheum Dis 2009;68:1094-9.