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Application of Multi-Omics Analysis in Periodontitis

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Abstract:

Periodontitis is a highly prevalent chronic inflammatory disease characterized by the progressive destruction of the tooth-supporting tissues and is closely associated with systemic health conditions. The complex and heterogeneous pathogenesis of periodontitis necessitates the adoption of comprehensive approaches to elucidate its molecular mechanisms. The advent of high-throughput omics technologies has revolutionized biomedical research, thereby enabling integrative multi-omics analysis to provide a holistic view of biological systems. This review aims to synthesize recent advances in the application of multi-omics strategies—including genomics, transcriptomics, proteomics, and metabolomics—in periodontitis research. This paper discusses how these approaches have elucidated the etiopathogenesis, identified novel diagnostic and prognostic biomarkers, and revealed potential therapeutic targets. Furthermore, this research explores the emerging role of artificial intelligence in integrating and interpreting complex multi-omics datasets. The conclusion underscores that multi-omics integration is pivotal for advancing personalized dentistry and precision medicine in periodontitis management, albeit challenges in data standardization and clinical translation remain to be addressed.

Keywords: Periodontitis; Multi-Omics; Biomarkers; Pathogenesis

1. Introduction

Periodontitis is a chronic inflammatory disease caused by dental plaque biofilm. It results in the loss of periodontal connective tissue attachment and progressive alveolar bone resorption, and serves as the primary cause of tooth loss in adults[1,2]. Its pathogenesis is complex, resulting from the interplay of dysbiosis of the microbiota, abnormal host immune inflammatory responses, genetic susceptibility, and environmental factors (such as smoking and diabetes) [3,4]. Traditional single research methods struggle to fully reveal its complexity. In recent years, the rapid advancement of omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, has provided a powerful tool for the in-depth

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investigation of periodontitis at the systemic level[5,6]. By integrating multi-omics data, researchers can construct a more comprehensive molecular network map of the disease, thereby gaining a deeper understanding of the dynamic processes underlying the onset and progression of disease.

This paper aims to review the recent advances in the application of multi-omics analysis techniques in periodontitis research over the past five years (2019–2024). The significance of this study resides in systematically synthesizing and summarizing the latest achievements of multi-omics approaches in the field of periodontitis, offering novel insights and actionable directions for future basic research and clinical translation, and facilitating the advancement of precision prevention, diagnosis, and treatment of periodontitis.

2. Introduction to Multi-omics Approaches

The core initiating factor of periodontitis is the dysregulation of the microbial community within dental plaque biofilm. The enrichment of specific pathogens (such as Porphyromonas gingivalis, Fusobacterium nucleatum, and Treponema denticola) disrupts host-microbiome homeostasis[7,8]. The host's excessive immune response to microbial challenges is a key driver in tissue destruction. Immune cells, such as neutrophils and macrophages, are activated and release large quantities of inflammatory mediators (such as IL-1β, IL-6, TNF-α), matrix Metalloproteinases (MMPs), and osteoclast-activating factors (such as RANKL), ultimately leading to the degradation of periodontal tissues and bone resorption[9,10]. An individual's genetic background (such as gene polymorphism) influences their susceptibility to periodontitis [11]. Meanwhile, environmental factors including smoking, psychological stress, and especially diabetes significantly increase the risk and severity of periodontitis[12,13].

Investigating Genetic Variation and Microbial Community Composition Genomics has identified host genetic variants associated with susceptibility to periodontitis via genome-wide association studies (GWAS) [14]. Metagenomics, on the other hand, involves directly sequencing all DNA present in oral samples, thereby enabling the comprehensive analysis of microbial species, functions, and antibiotic resistance genes in both healthy and diseased periodontal sites [15, 16].

Elucidating Gene Expression Regulation Transcriptomics (such as RNA-seq) detects gene expression differences across the entire genome at the mRNA level, thereby revealing signaling pathways that are activated or suppressed during periodontitis, including those related to inflammatory responses, immune responses, and tissue repair [17, 18].

Functional Effector Molecules Proteomics (such as mass spectrometry) directly identifies and quantifies protein expression profiles in gingival crevicular fluid (GCF), periodontal tissues, or saliva, thus revealing functionally relevant proteins associated with disease activity and potential therapeutic targets [19, 20].

Reflecting Terminal Physiological States Metabolomic analysis of small-molecule metabolites—such as organic acids, lipids, and amino acids—ultimately reflects the biochemical activity states during periodontal pathophysiological processes, thereby serving as a crucial bridge that links genotype to phenotype [21, 22].

Integrating multi-omics data is not merely a simple aggregation of datasets, but rather involves linking molecular data from different levels via bioinformatics methods to construct causal networks—thus facilitating a more systematic and in-depth understanding of the disease. [23, 24].

3. Specific Applications of Multi-Omics Analysis in Periodontitis Research

3.1 Applications of Genomics and Metagenomics

GWAS have identified multiple genetic loci associated with susceptibility to AgP and CP. For instance, single nucleotide polymorphisms (SNPs) localized within the GLT6D1 and SIGLEC5 genetic loci have been consistently demonstrated to exhibit a significant association with periodontitis risk in European and Asian populations [25]. These genes primarily play pivotal roles in immune regulation and inflammatory responses. For instance, SIGLEC5 encodes a sialic acid-binding immunoglobulin-like lectin that is predominantly expressed on myeloid cells and negatively regulates immune cell activation. Its dysfunction may result in uncontrolled inflammation [26]. Metagenomics employs shotgun sequencing to comprehensively analyze the microbial community composition and functional potential within subgingival plaque. Research indicates that periodontitis is not caused by a single pathogen, but rather by a significant increase in the relative abundance of bacteria belonging to the "red complex," represented by Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, which is accompanied by an ecological imbalance involving the synergistic interactions of multiple species [27]. Functional analysis has revealed that periodontal pathogenic

bacteria exhibit a significant enrichment of genes encoding virulence factors (such as gingipain and leukotoxin), peptidases, and host immune evasion mechanisms, whereas genes responsible for commensal bacterial survival are downregulated [28]. In recent years, the virome—particularly bacteriophages (phages)—has also been integrated into the research framework via metagenomics as a key factor that regulates bacterial community structure.

3.2 Transcriptomics Applications

Transcriptomics utilizes RNA sequencing (RNA-seq) technology to reveal changes in gene expression profiles at the systemic level within periodontal tissues or immune cells under disease states, thereby providing a dynamic perspective for understanding host response mechanisms. Transcriptomic analysis of gingival tissues from periodontitis patients has revealed strong activation of innate immune and inflammatory response pathways. For example, the expression of genes associated with the NF-κB signaling pathway, cytokine-cytokine receptor interactions (such as the IL-17 signaling pathway and TNF signaling pathway), the NOD-like receptor signaling pathway, and the complement system was significantly upregulated [29]. These findings confirm at the molecular level that periodontitis is a disease characterized by an excessive immunoinflammatory response. Transcriptomic analysis of peripheral blood immune cells has also revealed alterations in the systemic immune status of periodontitis patients, thereby providing a mechanistic explanation for the association between periodontitis and systemic diseases such as atherosclerosis and diabetes [30]. These findings provide a theoretical foundation for intervening in these key pathways.

3.3 Proteomics Applications

As the direct executors of biological functions, proteins are the primary focus of proteomics. Proteomics enables the direct identification and quantification of altered effector proteins in periodontitis, thus making it one of the most effective approaches for discovering biomarkers with diagnostic utility. Gingival crevicular fluid (GCF) and saliva serve as ideal sample sources for proteomic analysis owing to their non-invasive or minimally invasive collection methods. High-throughput mass spectrometry studies have identified numerous differentially expressed proteins in the gingival crevicular fluid (GCF) and saliva of periodontitis patients. Among these, proteins derived from neutrophils including S100A8, S100A9 (calcitonin gene-related protein), matrix metalloproteinases including MMP-8 and MMP-9, cathepsin G, and myeloperoxidase (MPO) were significantly elevated [31, 32]. These proteins are directly involved in extracellular matrix degradation and inflammatory processes, with their expression levels significantly correlated with periodontal clinical parameters such as probing depth and clinical attachment loss. Notably, MMP-8 has been extensively validated as a highly sensitive and specific biomarker for the diagnosis of periodontitis and the monitoring of disease activity. In addition to identifying biomarkers, proteomics has also elucidated novel pathological mechanisms. For example, analysis of post-translational modifications of proteins—such as phosphorylation and citrullination—reveals that these modifications are integral to periodontitis signaling pathways and autoimmune responses [33]. Furthermore, through proteomic analysis of periodontal tissues themselves, researchers identified protein expression alterations associated with impaired tissue repair capacity and defective epithelial barrier function, offering new insights into the imbalance between periodontal tissue destruction and repair.

3.4 Metabolomics Applications

The metabolome acts as a bridge between genotype and phenotype. By analyzing changes in small-molecule metabolites, metabolomics directly reflects the ultimate biochemical state during the pathophysiological processes of periodontitis. Metabolomic analysis of saliva, gingival crevicular fluid (GCF), and serum (typically employing nuclear magnetic resonance or liquid chromatography-mass spectrometry) has revealed a distinct metabolic profile in patients with periodontitis. Studies have shown that compared with healthy individuals, patients with periodontitis exhibit significantly elevated levels of short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate in their oral samples [34]. These SCFAs are products of carbohydrate fermentation by oral anaerobic bacteria. Among them, butyrate not only serves as an energy source but also modulates the epigenetic state of host cells and inhibits histone deacetylases, thereby further exacerbating epithelial barrier dysfunction and promoting inflammatory responses. Additionally, amino acid metabolism is also significantly disrupted. For example, elevated levels of proline, phenylalanine, and tyrosine in periodontitis patients may reflect enhanced tissue destruction and protein degradation. Lipid metabolomics analysis revealed altered levels of inflammation-associated polyunsaturated fatty acid metabolites, specifically arachidonic acid derivatives (prostaglandins, leukotrienes) [35]. These specific metabolite profiles not only facilitate the distinction between healthy and diseased states but may also serve as sensitive indicators for monitoring treatment response.

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3.5 Multi-omics Integration Applications

Single-omics approaches are limited to capturing a singular facet of biological processes, whereas integrated multi-omics analysis facilitates the construction of causal networks, offering a more systematic and profound understanding of disease. For instance, a pioneering study that integrated metagenomic and metabolomic data demonstrated that microbial taxa enriched in periodontitis exhibited a positive correlation with the concentrations of specific metabolites—particularly butyrate—in gingival crevicular fluid (GCF). By constructing a microbial-metabolite interaction network, this study proposed a mechanistic model wherein specific pathogens directly regulate the local microenvironment through their metabolic activities, and in turn influencing host immune responses [36]. Another landmark study simultaneously profiled the transcriptome and proteome of periodontal tissues. The results indicated that while the expression trends of most mRNAs and their corresponding proteins are consistent, post-transcriptional regulation was also prevalent. This integrated analysis enables more accurate identification of key targets that exhibit actual functional changes at the protein level, avoiding false positives that may arise from transcriptomic data alone. It further reveals that critical factors such as IL-1β may undergo fine-tuned regulation at the level of translational efficiency [37].

4. Conclusion

Multi-omics research is confronted with challenges such as sample heterogeneity, limited cohort sizes, lack of data standardization, high costs, and substantial computational and storage demands [38, 39]. Furthermore, bioinformatics algorithms for integrating multi-omics data necessitate further refinement.

Future research will increasingly focus on large-scale prospective cohorts, longitudinal sampling (for dynamic monitoring), and single-cell spatial multi-omics technologies (scRNA-seq, Spatial Transcriptomics) to decipher cellular heterogeneity and the periodontal microenvironment [40, 41]. The ultimate goal is to translate multi-omics discoveries into clinically actionable diagnostic tools (such as POCT tests), indicators for monitoring disease activity, and personalized treatment strategies (such as targeted therapies against specific pathways or microorganisms) [42, 43].

Multi-omics analysis technologies offer unprecedented opportunities for comprehensively and systematically understanding the complex nature of periodontitis. By integrating genomic, transcriptomic, proteomic, and metabolomic data, research has evolved from identifying individual molecular markers to gaining holistic insights into disease networks, and has significantly deepened our understanding of the microbial etiology of periodontitis, the host immune inflammatory response, and the interplay between the two.

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