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REVIEW
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Systems Biology in Periodontitis

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Systems biology is a promising scientific discipline that allows an integrated investigation of host factors, microbial composition, biomarkers, immune response and inflammatory mediators in many conditions such as chronic diseases, cancer, neurological disorders, and periodontitis. This concept utilizes genetic decoding, bioinformatic, flux-balance analysis in a comprehensive approach. The aim of this review is to better understand the current literature on systems biology and identify a clear applicability of it to periodontitis. We will mostly focus on the association between this condition and topics such as genomics, transcriptomics, proteomics, metabolomics, as well as contextualize delivery systems for periodontitis treatment, biomarker detection in oral fluids and associated systemic conditions.

Keywords: systems biology, periodontitis, genetic decoding, genome, transcriptome, proteome, metabolome, meta-transcriptome

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INTRODUCTION

Systems biology is a promising scientific discipline that aims at understanding the biological organisms and the multilevel interconnections between their different cell constituents (1, 2). It utilizes different quantitative, experimental and computational methods to decode genetic information, protein activities and signaling pathways in the cells, tissues, and organisms (3–5).

An important applicability of this field is the tracking of molecular changes that occur in pathological events (6) such as periodontitis. Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterized by progressive destruction of the tooth-supporting apparatus (7).

In order understand the pathogenesis of periodontitis, studies have reported isolated biological regulatory mechanisms instead of utilizing integrated systems (8–12). Biological systems study models allow for the integrated investigation of local host factors, microbial composition, in periodontal tissue as well as systemic immune response (13). It better replicates biology of the biofilm-gingival interface in specific patients and provides insight into their clinical management (6, 14).

Unfortunately, this approach is in its infancy, and there is limited data available, especially as it relates to periodontitis. In this review, we will mostly focus on systems biology as an emerging approach to periodontal studies, with the potential of bringing accurate diagnosis and treatment closer to a translational reality, as well as creating a scientific basis for future studies to elucidate and enrich this thematic.

KEY PRINCIPLES OF SYSTEMS BIOLOGY

Systems biology is a new discipline that studies the molecular diversity of living systems, by identifying principles and patterns and integrating them through complex models of regulatory mechanisms (15). It involves computational analysis, mathematics,

and physical concepts (1, 2). Furthermore, it focuses on complex interactions within biological systems, using a holistic approach to conducting modern research (14).

Despite being a new field and integrating biological systems in its entirety, systems biology can also be analyzed from the perspective of traditional scientific methodology including test-based hypothesis (3). When we think about the differences between healthy conditions and illnesses, it is certainly expected that there are different protein expressions in these seconds due to the disturbances suffered at the genetic level. This is what systems biology is based on when addressing inflammatory processes and diseases in general (16). The investigation encompasses genomics, transcriptomics, proteomics, metabolomics with the goal of data integration. In this review we will discuss each one in detail with the objective of intertwining all of them.

The investigation of candidate molecular biomarkers for the diagnosis and prognosis of inflammatory diseases through bioinformatics analysis of gene expression datasets is an example of systems biology application (11). Specifically, regarding oral diseases, in the last decade many studies have been using systems biology in their searches, although this knowledge field is not completely explicit (17–21). Furthermore, recent advances in sequencing technologies allow researchers to profile disease-associated microbial communities, quantify microbial metabolic activities and host transcriptional responses, and correlate to oral diseases such as periodontitis (22–25). The potential limitations in systems biology refer precisely to the scarce literature and the diversity of imprecise definitions. Classic terms such as "a new type of biology" or "the successor to molecular biology" cannot fully explain this new discipline that aims to integrate biology and technology from different points of view (1, 3). These limitations could be overcome by an extensive and continuous discussion and, even more, by a formal meeting between biologists and scientists from different areas with the aim of standardizing concepts, classifications and objectives of this complex knowledge.

SYSTEMS BIOLOGY CONCEPTS IN PERIODONTITIS

Systemic Decoding of Periodontal Inflammation

According to the current model of periodontitis pathogenesis, the complex interactions between plaque bacteria, host genetic factors and acquired environmental stressors must be considered (25, 26). Although bacteria present in the plaque biofilm initiate inflammation, intrinsic host factors and environmental stressors modulate the magnitude, duration, and extent of an inflammatory response (27, 28). Understanding the molecular mechanisms underlying the pathogenesis as well as the development of efficient therapeutics is even more important since periodontitis is linked to other metabolic and/or systemic diseases including diabetes, cardiovascular diseases, and rheumatoid arthritis (23, 29–31). Currently, many studies have evaluated genomics, proteomics and metabolomics in an isolated and non-integrated manner, therefore, combining all these approaches in a systematic way will allow us to better understand and treat the disease.

Genomics in Periodontitis

The identification of the causal variant(s) that increase the susceptibility/resistance to periodontitis can be done by Genome-wide Associated Studies (GWAS). In fact, GWAS has provided insight into novel loci and biological processes plausibly implicated in this complex biofilm-dependent disease (31–38) through human and animal studies (17, 39, 40). Other studies have also discussed the current knowledge on genomics considering inflammatory cytokines and polymorphisms related to periodontitis (35, 36, 41, 42).

The meta-analysis by Munz et al. (43), that included 16 studies comprising 5,095 cases and 9,908 controls, identified novel risk loci of periodontitis. The same group performed a GWAS meta-analysis on coronary artery disease and periodontitis. The study revealed that the molecular pathway shared by these two conditions involves a novel risk locus (VAMP8) (44).

The use of GWAS to understand periodontitis has suggested that there are many potential contributors to periodontitis, reinforced that some genes should be further investigated and validated the importance of many genes that we already know are relevant to periodontitis. Moving forward the integration of data obtained from GWAS in patients and in animal models with the microbiome and proteome will allow a broader view in the mechanisms underlying periodontitis and may serve as a foundation for a more personalized treatment approach (17, 40, 45).

Transcriptomics in Periodontitis

Transcriptomics refers to the complete set of gene transcripts or RNA transcribed in a given cell type, tissue or organism for a specific physiological or pathological condition (46). It studies and interprets the key functional output of the genome, comparing cells or tissues under defined conditions or disease states to identify changes in gene expression (47–49). Transcriptomics can efficiently narrow down candidate genes associated with multifactorial diseases, assist in the investigation of underlying mechanisms of diseases and the identification of biomarkers for diagnosis and prognosis (6, 11, 50, 51). Studies evaluating the transcriptome of periodontitis have been performed human and in animal models (**Table 1**).

When evaluating the transcriptome, clinical studies have observed increased periodontal inflammation due to increased oxidative stress, innate immune response regulation (57), and collagen degradation (18, 23, 58, 60). For instance, Suzuki et al. (11) investigated a candidate molecular biomarker for diagnosis and prognosis of periodontitis through bioinformatic analysis of pooled microarray gene expression datasets in Gene Expression Omnibus (GEO). The study observed that IL-1β is one of the upstream regulators of CSF3 and CXCL12, both up-regulated and related to the inflammation process and bone loss in periodontitis (**Table 1**) (11).

A clinical study performed RNA sequencing (RNA-seq) of peripheral blood monocytes (PBMs) in periodontitis cases and

TABLE 1 | Transcriptomics in periodontal inflammation by RNA sequencing data.

Reference	Study design	DNA extracted from	Technology	DEGssequenced	Protein regulated	Periodontitis groups outcome
Maekawa et al. (52)	*In vivo*	Gingival tissue	Illumina MiSeq	Innate immune response-related genes (S100a8 and S100a9)	CTSK and MMP9	Neutrophil chemotaxis
Liu et al. (53)	Clinical	Peripheral blood monocytes	Illumina TruSeq	FACR and CUX1	TNF and lipopolysaccharide	↑PBMs gene expression, endocytosis, cytokine production and apoptosis
Corrêa et al. (54)	Clinical	Subgingival dental plaque	Quick-gDNA MicroPrep	16S rRNA	IL-6, IL-17 and IL-33	↑Periodontal inflammation, severe SLE scores
Zhu et al. (55)	*In vivo*	Bone marrow mononuclear cells	Agilent 2100 Bioanalyzer	Runx2 e Ocn	TLR4, AP1 e IL-6	↑Alveolar bone destruction ↓Osteogenesis
Wang et al. (56)	*In vivo*	Periodontal tissue	Illumina HiSeq	SLIT2	MAPK	↑Inflammation, immune cells infiltration, M1 macrophage polarization, osteoclastogenesis and alveolar bone loss
Suzuki et al. (11)	Clinical	Gingival tissue	GEO2R	CSF3 and CXCL12	↑IL1B	↑Bone resorption and inflammation
Guo et al. (21)	*In vivo*	Periodontal tissue	NanoDrop 2000	↓miRNA-218	↑Mmp9	↑Collagen Types I and IV degradation, RANKL-induced osteoclast formation and inflammatory factors levels
Kim et al. (23)	Clinical	Gingival tissue	Illumina HiSeq 2000	CSF3, MAFA, CR2, GLDC, SAA1, LBP, MME, MMP3, MME-AS1, and SAA4	↑ICAM1, MMP13, LYN, CSF3, MMP3, LBP, and CXCL2. ↑ IL6, IL19 (slightly increased)	Inclusion of EDB exon and skipping of exon 2 in BCL2A1
Zhou et al. (57)	Clinical	Gingival tissue	Genome-wide sequencing	FAM126B, SORL1, PRLR, CPEB2, RAP2C, and YOD1	FAM126B, SORL1, PRLR, CPEB2, RAP2C, and YOD1	The lncRNA-miRNA-mRNA interaction regulated signaling pathways, oxidative stress and innate immune process
Horie et al. (58)	Clinical	Gingival tissue	CAGE-seq	DLX5 and RUNX2	Collagen	Altered expression of ECM and collagen degradation
Guo et al. (59)	*In vivo*	Gingival tissue	HiSeq 2000 System	H19	p-AKT	Activation of autophagy via AKT pathway
Qian et al. (60)	Clinical	Gingival tissue	scRNA-seq	HLA-DR, CXCL13+, NLRP3+ genes	HLA-DR, CXCL13+, NLRP3+	↑Communication between macrophages and B/T cells

DEGs, Differentially Expressed Genes; SLE, Systemic Lupus Erythematosus; CTSK, Cathepsin K; MMP9, Matrix Metallopeptidase 9; TNF, Tumor Necrosis Factor; PBM, Peripheral Blood Monocytes; TLR4, Toll-like receptor 4; AP1, Activator protein 1; IL-6, Interleukin-6; MAPK, Mitogen-activated protein kinase; ICAM1, Intercellular Adhesion Molecule 1; MMP13, Matrix metallopeptidase 13; LYN, Tyrosine-protein kinase Lyn; CSF3, Colony Stimulating Factor 3; LBP, Lipopolysaccharide binding protein; CXCL2, Chemokine (C-X-C motif) ligand 2; CAGE, Cap Analysis of Gene Expression; EDB, Extra domain B; BCL2A1, BCL2-related protein A1; SORL1, Sortilin-related receptor; PRLR, Prolactin Receptor; CPEB2, Cytoplasmic polyadenylation element-binding protein 2; p-AKT, Protein kinase; GEO2R, Gene Expression Omnibus database; HLA-DR, Human Leukocyte Antigen – DR isotype; ECM, Extracellular matrix.

identified 380 genes transcribed from differentially expressed isoforms (DEx) and suggested a more functionally active monocyte transcriptome in periodontitis patients compared to healthy individuals. Furthermore, several of the genes identified as associated with periodontitis are known for interacting with invading microorganisms (53).

In murine models of periodontitis, transcriptomics have associated: (a) proteins present in bone marrow cells with increased alveolar bone destruction and decreased osteogenesis (55); (b) MAPK with increased inflammation, M1 macrophage polarization, osteoclastogenesis (56) and (c) Mmp9 with collagen type I and IV degradation, besides RANKL-induced osteoclast formation, both in the DNA extracted from periodontal tissue (21).

For instance, in trying to identify the relevant differentially expressed genes and clarify the mechanism underlying alveolar bone loss using ligature-induced periodontitis in mice, Maekawa et al. (52) performed an enrichment analysis of gene ontology terms. This study revealed that neutrophil chemotaxis and inflammatory responses were significantly enriched in the gingival tissues around teeth where periodontitis was initiated through a ligature model (52).

A study aiming to obtain insights into periodontitis etiology combined GWAS and transcriptomic data from mouse and

humans. This study was able to further identify two sets of periodontitis (chronic and aggressive) (61).

More recently, the literature has shown advanced technologies to perform single-cell RNA sequencing (scRNA-seq) in terms of detection of periodontitis and its specific changes. While Takada et al. (62) identified that the Mohawk homeobox transcription factor (Mkx) expressed in the periodontal ligament of Wistar rats was involved in ankylosis and periodontitis, Chen et al. (63) investigated the osteoimmunological microenvironment in the periodontitis development by scRNA-seq and identified more than 50 thousand cells isolated from healthy patients, individuals with severe chronic periodontitis, and others with severe chronic periodontitis. Among other findings, enrichment of TNFRSF21+ fibroblasts with high expression of CXCL13 was detected in patients with periodontitis compared to healthy subjects.

In addition to these authors, Agrafioti et al. (64) also used single-cell RNA-sequencing and decoded the role of macrophages in periodontitis and type 2 diabetes. They observed high expression of a subunit of NF-κB called RELA in gingival macrophages of patients with periodontitis with diabetes.

Transcriptomics has advanced our field and is necessary to help understand periodontitis pathogenesis and to facilitate the development of more precise biomarkers for disease prevention, diagnosis and prognosis. The current task is to combine and utilize the resulting data sets to benefit patient care (65). Additional related studies and their applied technology can be seen in **Table 1**.

Proteomics in Periodontitis

Proteomics is the study of the entire set of proteins expressed by a cell, tissue or a organism at a particular state/time (66–68). It supplements the other "omics" technologies such as genomic and transcriptomics (69). In recent years, several studies have discussed the use of proteomics in periodontitis (65, 70–73).

Many animal studies have performed proteomics analysis of periodontitis (74–78). For instance, it has identified interleukin 4 (IL-4) as having protective role in bone destruction due to its anti-osteoclastogenic action (77).

Human studies evaluating periodontitis through proteomics have identified many proteins as being different in health and diseases (79–81). For instance, Bostanci el al. evaluating gingival crevicular fluid identified that one hundred and nineteen proteins are different between health patients and disease subjects (82). Mertens et al. evaluating salivary samples identified hemopexin, plasminogen and α-fibrinogen in the saliva of patients with periodontitis compared with healthy subjects (81). A recent case-control study analyzed the salivary proteome of individuals with chronic periodontitis and observed that there is an increase in acidic proline-rich phosphoprotein, submaxillary gland androgen-regulated protein, histatin, fatty acid binding protein, thioredoxin and cystatin in patients with periodontitis (79).

The growing use of proteomic techniques has allowed our field to better understand the pathogenesis and biomarkers identification for diagnosis and prognosis.

Metabolomic Approaches to Periodontitis

Periodontal inflammation triggers biological reactions that can consequently be expressed in metabolic changes (80, 83). The most common way of analyzing a metabolic network is using flux-balance analysis, which involves calculating the flow of metabolites through the network in steady state (84–86). In recent years, the metabolic networks of whole organisms have become available and, for instance, the metabolism of intestinal microbial communities has been reconstructed (87). In oral biology, despite extensive studies published on the variation in the oral microbiota and metabolic profiles of patients with periodontitis, information is still lacking regarding the correlation between host-bacterial interactions and biochemical metabolism (88).

Thus far, there have been several longitudinal, cross-sectional and animal studies evaluating the relationship between periodontitis and metabolic components behavior (63, 88–90). When periodontal tissue is in an inflammatory state, inflammatory factors such as cytokines, bacterial antigens, various cells, metabolites, and other degradation products are released in the gingival crevicular fluid (GCF) (89, 91, 92). By analyzing the oral microbiome and oral metabolome in periodontitis, in addition to identifying biomarker molecules, a recent cross-sectional study detected functional changes in basic metabolism including vitamins, energy and cofactor (88).

Another cross-sectional study analyzed metabolic profiles in individuals with aggressive periodontitis and identified, among other differences, an increase in dehydroascorbic acid and a decrease in thymidine in gingival crevicular fluid when compared to healthy individuals (93).

Marchesan et al. (94) performed an analysis of microbiome microarray data and metabolite data from saliva and assessed the relationships among plaque microbial composition, salivary bacterial metabolites and periodontitis phenotypes in a well-established stent-induced biofilm overgrowth clinical model. Several newly identified putative periodontal pathogenic species in the *Synergizes* and *Treponema* phyla were significantly associated with periodontitis parameters (94). The differential detection of biomarker metabolites in the GCF, in addition to being an excellent diagnostic tool, can also be an important strategy in the treatment of periodontitis (88).

In addition to human studies, *in vivo* studies have also applied methodologies based on metabolomic approaches. For example, an interesting animal study determined the metabolic effects of periodontitis beyond the mouth such as decreased plasma lysolipid metabolites, increased liver bile acid synthesis, decreased brain glucose and increased cysteine and changes in redox homeostasis in the heart (90).

Applying a similar method, another animal study validated the association between high fat diet (HFD) and periodontitis in arginine metabolism (related to M1/M2 macrophage phenotypes) and observed that HFD was able to increase L-arginine levels. Periodontitis alone showed enhanced spermidine, a product related to M2 macrophages (63). Additional related studies can be seen in **Table 2**.

TABLE 2 | Some metabolic approaches in periodontitis.

Authors	Study design	Population	Sample	Technology	Metabolic component and periodontitis outcomes
Pei et al. (88)	Cross-sectional	30	GCF	Gas chromatography-mass spectrometry	↑Citramalic acid and N-carbamyl Glutamate ↓Carbohydrate metabolism
Ma et al. (89)	Cross-sectional	96	GCF and serum	Liquid chromatography/mass spectrometry	↑Pseudouridine, l-phenylalanine, p-hydroxyphenylacetic acid and CRP ↑IL-6patients with ESRD
Ilievski et al. (90)	*In vivo*	20 mice	Plasma, liver, brain and hearth	Liquid chromatography/mass spectrometry	**Plasma**: ↓5-methylthioadenosine (MTA) ↓Citrulline **Liver:** ↑7-hydroxycholesterol ↑S-methylcysteine **Brain:** ↓Glucose ↓Fructose-6-phosphate **Heart:** ↑Cysteine ↑Cysteine-glutathione disulfide
Chen et al. (63)	*In vivo*	42 mice	Gingival Tissue	Liquid chromatography/mass spectrometry	**HFD + Periodontitis**: ↑L-arginine ↑L-ornithine ↑L-citrulline **Periodontitis alone**: ↑Spermidine (M2-related product)
Chen et al. (93)	Cross-sectional	40 patients	GCF and serum	Gas chromatography-mass spectrometry	**GCF**: ↑Noradrenaline ↑Uridine ↑α-tocopherol ↑Dehydroascorbic acid ↑Xanthine ↑Galactose ↑Glucose-1-phosphate ↑Ribulose-5-phosphate ↓Thymidine ↓Glutathione ↓Ribose-5-phosphate **Serum**: ↑Serum urea ↑Allo-inositol Glutathione ↓2,5-dihydroxybenzaldehyde ↓Adipic acid ↓2-deoxyguanosine

GCF, Gingival Crevicular Fluid; CRP, C-reactive protein; ESRD, End-stage renal disease; AI, Inflammation anemia; MDA, Malondialdehyde; TOS, Total oxidant status; TNF, Tumor Necrosis Factor; PDGF-bb, Platelet-derived growth factor; VEGF, Vascular endothelial growth factor.

Optimizing Drug Delivery Systems for Periodontitis Treatment

Classic conventional therapy for periodontitis treatment, including mechanical plaque removal, is sometimes unable to eliminate bacterial debris in hard-to-reach areas. The literature is rich in studies that defend and highlight the role of complementary therapies whose proposal is precisely to assist in this bacterial control or immune-regulation, including chemical drugs, probiotics, photodynamic therapy, and systemic antibiotics (95–99).

In terms of technological innovations and broader approaches focused on systems biology, advanced drug delivery strategies using biodegradable nanocarriers have been proposed to avoid problems such as toxicity and antibiotic resistance in periodontitis treatment (100). Among them, a recent study developed computer simulations using an in situ localized nanogel drug delivery system for periodontitis and noted that the formulated nanoemulgel exhibited a remarkable release of 92.4% of quercetin at the end of 6 h, as compared to that of pure quercetin-loaded gel (<3% release) (101). The versatility of distinct nanocarriers allowing for improvement of their loading and releasing capabilities could be used for microbiological control, periodontal regeneration, and/or immunomodulation (100).

Systems biology approaches optimizing drug delivery have been described by several authors will most likely emerge as alternatives to the classical treatment of periodontitis (102–107).

Utilization of Oral Fluids for the Detection of Biomarkers and Microbiome

Oral fluids may offer the basis for patient-specific diagnostic tests for periodontitis because it can be easily collected and contains local and systemic-derived biomarkers. Among them, there is the GCF which consists of an inflammatory exudate originating from the gingival plexus of blood vessels in the gingival corium, subjacent to the epithelium lining of the dentogingival space (91). In clinical health, the periodontium secretes an inflammatory infiltrate within the crevicular sulcus (19, 45, 108, 109). In pathological situations, such as periodontitis, as the disease progresses, the GCF volume increases and inflammatory mediators including cytokines, arachidonic acid metabolites and enzymes are upregulated (110).

An ever-expanding pool of GCF proteins associated with periodontal health or disease has been cataloged over the years, particularly with the recent implementation of proteomic technologies which provide a broad qualitative and quantitative insight of the proteins present in gingival crevicular fluid (82).

In a recent study, Kim et al. performed proteomic analysis of GCF and identified galectin-10 as a biomarker for periodontitis (111). Batschkus et al., in turn, aiming to identify and quantify proteins obtained from CGF of patients with periodontitis, observed three hundred and seventeen different proteins trrough by SDS-PAGE and high-resolution mass spectrometry (108).

A similar study, published by Marinho et al. compared the relative abundance of 104 proteins in the GCF from individuals with type 2 diabetes mellitus with and without periodontitis. In patients with diabetes there was an increase in titin, neutrophil elastase and myeloperoxidase while cathelicidin antimicrobial peptide decreased in periodontitis cases and annexin decreased in healthy patients (112).

The use of salivary biomarkers has been heavily employed in recent years, including in omics approaches because it can be easily collected and it has low cost (113). For instance, specific host- or bacteria-derived biomarkers detected in saliva could indicate the presence or progression/remission of periodontitis (70, 79, 114, 115). Other recent studies made discoveries in the proteomics field and saliva diagnosis, including multiplexing platforms development (116) and rapid-test-kit with Shotgun proteomics (73).

Systemic Conditions, Periodontitis and Systems Biology

Systemic diseases with increased inflammation are frequently linked to increased risk of periodontitis (117, 118). Some of the systemic conditions linked to periodontitis described below are diabetes mellitus, cardiovascular diseases, metabolic syndrome and systemic lupus erythematosus.

Diabetes mellitus, a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (119), shares a bidirectional relationship with periodontitis (120). Because of that, there have been many studies that addressed such conditions simultaneously under different clinical and biological perspectives and with different study designs (121–125). As an example, sequencing 16S rDNA in subgingival dental plaque from patients with type 2 diabetes allowed the authors to quantify 110 metabolites and 415 lipids, but the most important findings were that the cross-omics correlation analysis revealed a novel microbial metabolic pathway and significant associations of host-derived proteins with periodontitis (126).

Other systemic conditions associated with periodontitis are cardiovascular diseases, whose incidence, especially coronary artery disease and atherosclerosis, have been increasing alarmingly (127–129). Atherosclerosis and periodontitis utilize common inflammatory signaling pathways and in addition, bacteria associated with periodontitis have been identified in atherosclerotic plaque specimens (92, 130–132). A review by Mirnejad et al. focused on the most important bacterial species involved in cardiovascular diseases and periodontitis presented recent findings about the proteomic evaluation of virulence factors of these bacteria (132). Another review by Pietiäinen et al. (133) summarized possible molecular mediators between the dysbiotic oral microbiota and atherosclerotic processes, and, among others, included a study that performed Pyrosequencing of bacterial 16S rRNA genes in oral swabs which did not reveal significant differences between patients with atherosclerosis and controls (133, 134).

System biology studies have also been able to link metabolic syndrome, a group of conditions defined by the presence of obesity, dyslipidemia, hypertension, and deglycation leading to an increased risk of diabetes and cardiovascular disease (118) to periodontitis (135, 136). An association with systemic lupus erythematosus (SLE) and periodontal disease has also been observed by sequencing the V4 region of the 16S gene (54).

Studies focusing on how periodontal inflammation may affect systemic conditions are necessary, not only to investigate the mechanisms underlying this inflammatory process, but also to establish therapeutic strategies (137). Applying the concepts of system biology in these investigations is as important as the need to clarify this new discipline and integrate it with classical disciplines such as periodontal medicine and systemic diseases.

Some possible future directions for systems biology in periodontitis may include computer-aided design software development and finite element analysis for inflammatory assessment, bone loss, and bone regeneration, as well as innovative computed radiology and ultrasound for tissue regeneration analysis.

In the clinical field of implantology there is a remarkable applicability of new technologies, including computed radiology and resonance frequency analysis (RFA) of osseointegration around implants. An example of this is the Osstell® device, which consists of a small piezoelectric transducer in which the RFA is automatically converted into an index that informs the Implant Stability Coefficient via software (138).

CONCLUSIONS

This review analyzed different studies in periodontology that have applied partial systems biology concepts in their thematic and methodological approaches. Even though, it is an emerging

area, it is strongly intertwined with what has been studied for years in terms of periodontitis diagnosis and treatment. Going from traditional biological approaches to a systemic investigation model, adding OMICS technology, has already taken important steps. Although translating the OMICS data into clinical approaches is challenging, the oral microbiome plays a key role for different systemic or oral conditions such as periodontitis. Therefore, profiling subgingival bacterial communities by omics methods is a great tool for early detection of periodontitis biomarkers. It is suggested that new studies need to be developed not only to enrich this topic, but also to better investigate periodontitis and other oral conditions.

AUTHOR CONTRIBUTIONS

DS and SM conducted bibliographic research and manuscript writing. FP contributed to the writing and guided the manuscript. All authors contributed to the article and approved the submitted version.

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