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REVIEW ARTICLE

WILEY ORAL DISEASES

Understanding the pathophysiology behind chairside diagnostics and genetic testing for IL-1 and IL-6

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Abstract

In order for chairside diagnostic testing to make an impact on dental therapy, practitioners require a better understanding of genetic mutations contributing to the pathophysiology of periodontal disease. Commensal and pathogenic bacterial colonization in oral cavity tissues produces a cascade of proinflammatory signaling pathways ultimately detrimental to host tissues. Resolving inflammation is a multifactorial process involving the downregulation of proinflammatory cytokines while allowing commensal bacterial levels to return to normal. Because of the complicated nature of commensal bacteria and oral health homeostasis, the emphasis of dental therapy should place renewed focus on limiting destructive inflammation rather than solely eliminating bacteria. Salivary diagnostics are an easy, non-invasive way to assess inflammatory markers. Inflammatory cytokine levels can help determine the subclinical health of a patient, showing the transition from health to gingivitis, or periodontitis, prior to clinical presentation. Single nucleotide polymorphism mutations can aid in determining increased risk of developing periodontitis. Taken together, and alongside regular clinical evaluations, chairside diagnostics help individualize treatment plans to slow, or halt, the progression of disease—before tissue destruction can take place. While more studies are needed analyzing specific mutations across periodontal categories, chairside diagnostics present an exciting adjunct to improve patient care.

KEYWORDS

diagnostic molecular pathology, inflammation mediators, interleukin-1, interleukin-6, periodontal disease, precision dentistry

1 | INTRODUCTION

As health professions move toward a predictable, personalized, and preventative precision approach in patient care, the field of dentistry should be no exception. The use of genetic testing in the diagnosis and treatment of disease is becoming more widespread and therefore easier to access and less expensive. To utilize chairside diagnostic testing in relation to treatment planning for periodontal diseases in a proper manner, health professionals first must understand what genetic mutations and inflammatory markers mean in the pathogenesis of periodontal disease. This commentary is written to assist health professionals in understanding the rationale for and current state of chairside diagnostic testing for clinical use in periodontal therapy.

2 | PERIODONTAL DISEASE PATHOGENESIS—OVERVIEW

Periodontal disease begins with a disruption of normal host/commensal bacteria homeostasis leading to an increase in colonization by periopathogenic microbes and triggering of the host's inflammatory responses which can lead to tissue destruction (Herrero et al., 2018; Van Dyke, 2017). The gingival sulcus is bordered by junctional epithelial (JE) cells which are loosely connected by hemidesmosome attachments creating a highly

TABLE 1 Properties and function of interleukin-1 and interleukin-6

Family members	**Sub Family IL-1:** IL-1a, IL-1b, IL-1Ra, IL-33 **Sub Family IL-18:** IL-18, IL-37 **Sub Family IL-36:** IL-36α IL-36β IL-36γ, IL-36Ra	**Biologic functions**	-Primarily associated with the innate immune response and damaging inflammation -Lack signal peptides and are found in cytoplasm as precursor molecules -Signals similarly to TLRs due to conserved Toll-IL-1 receptor (TIR) -Promote T-cells differentiation into Th17 cells	**IL-1α:** constitutive in many cells epith, endoth, and mesenchymal cells, nucleus, cytoplasm, cell membrane Active in precursor and mature forms Acts in the nucleus with a major role in Th2 responses Dual function cytokine: in nucleus — inhibits proinflammatory cytokine expression, in the cytosol — released as a DAMP to increase proinflammatory responses Also found in: endothelial and mesenchymal cells Integral membrane protein - critical for several IFN-γ activities, Synthesis might be dependent on regulatory activities of IL-1β Recombinant IL-1Ra (anakinra) blocks IL-1α and IL-1β signaling but increases incidence of infections
			Il-18: protective in inflammatory diseases Proinflammatory properties by increasing IFN-γ	
Expression	Macrophages Monocytes Neutrophils Hepatocytes Epithelial Cells		**IL-33:** Acts as a DAMP Similar functions as IL-1α Dual function cytokine: in the nucleus – binds chromatin causing shift to Th2 response Anti-inflammatory properties Potential role in Th1 Proinflammatory responses by increasing IFN-γ	**IL-1β:** potent pro-inflammatory molecule Induced by microbe-cell interactions, also auto-inducible Promotes migration of immune cells from blood to tissues Regulates Extra Cellular Matrix Induces expression of other proinflammatory cytokines Role in: autophagy, NLRP3 Inflammasome contains Caspase-1 which activates soluble precursor IL-1 β molecules Oral NLRP3 inhibitors reduce IL-1β mediated inflammation Stimulates CD4+ T cell responses Recombinant IL-1Ra (anakinra) blocks IL-1α and IL-1β signaling but increases incidence of infections
Acts on	T-Cells		**IL-37:** Anti-inflammatory prohibits innate inflammation Also expressed on: Synovial Cells, Tonsillar B Cells, Neoplastic Cells	
Sources	Da Silva et al. (2017), Dinarello, (2018a), Dinarello, (2018b), Turner et al. (2014).		**IL36:** Increased circulating levels and salivary gland expression in Sjogren's syndrome, Psoriasis, Rheumatoid Arthritis, Chron's Disease	

Family members	IL-6, IL-11, IL-31, ciliary neurotrophic factor, cardiotrophin-1, leukemia inhibitory factor, oncostatin M	**Biologic functions**	Has both Pro-inflammatory and Anti-inflammatory properties Produced in response to LPS-cell interactions Expression is increased in GCF, serum, and saliva in patients with chronic periodontitis Induced by IL-1β Induced by calprotectin Involved in hematopoiesis Causes activated B Cells to differentiate into Plasma Cells Stimulates IgG production Th2 cell activation, differentiation, and regulation T-regulatory cell activation, differentiation, and regulation Secretion of acute phase proteins in the liver Activates osteoclasts Induces bone destruction Induces collagen destruction Increases RANKL secretion Increases VEGF and MMP production IL-6 levels can indicate mortality risk in patients with coronary artery disease IL-6 levels can indicate risk of cardiovascular death in healthy patients Linked to Alzheimer's disease IL-17 secreted from Th17 cells works synergistically with IL-6 to increase inflammation
Expression	T-helper cells B Cells Macrophages Fibroblasts Endothelial cells Keratinocytes Hepatocytes		
Acts on	Activated B cells (Plasma cells)		
Sources:	Batool et al. (2018), Bostanci et al. (2017), Dekita et al. (2017), Kobayashi et al. (2016), Nagao et al. (2017), Nishikawa et al. (2017), Turner et al. (2014), Zhang et al. (2016).		

vascularized porous surface, through which immune cells can traffic and detect pathogenic bacterial signals (Darveau, 2010; Degasperi et al., 2018). JE cells produce E-selectin, Intercellular Adhesion Molecules, and Interleukin (IL)-8 to facilitate transit of immune cells through the sulcular tissue (Darveau, 2010). While neutrophils are often referred to as "resident" cells, there are approximately 30,000 neutrophils trafficking through the JE every minute (Darveau, 2010). Constant presence of immune cells leads to a controlled inflammatory state in human gingival tissues (Darveau, 2010). Periodontal tissues such as collagen type I, fibronectins, epithelial cells, and ligaments all produce cytokines and chemokines (e.g., IL-1α, IL-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, granulocyte–macrophage colony-stimulating factor, β-defensins, cluster of differentiation (CD)14, and lipopolysaccharide (LPS)-binding protein), to clear bacteria and bacterial components and regulate the ever-present inflammatory state (Darveau, 2010; Degasperi et al., 2018; Ramage et al., 2017). Bacterial early colonizers, such as Gram-positive (Gm+) bacteria *Streptococcus* species, produce hydrogen peroxide which prevents colonization of Gram-negative (Gm−) bacteria (Darveau, 2010; Herrero et al., 2018). The lipoteichoic acids (LTA) of Gm+ bacteria are recognized as pathogen-associated molecular patterns (PAMPS) by epithelial cells, neutrophils, and dendritic cells present in the gingival sulcus (Degasperi et al., 2018). These primary defense cells secrete proinflammatory cytokines and chemokines to prime the host immune response for bacterial invasion. Once subclinical inflammation has set in, resident pathogenic Gm− bacteria (*Porphyromonas gingivalis* and *Tanerella forsythia*) of the orange and red complex utilize the by-products of tissue breakdown (hemoglobin, collagen peptides, and plasma proteins) as nourishment and upset the homeostatic balance of the sulcus (Berezow & Darveau, 2011; Darveau, 2010; Herrero et al., 2018). With the increased colonization of pathogenic bacteria, pattern recognition receptors on periodontal tissue cells recognize bacterial components (e.g., DNA, fimbriae, flagella, peptidoglycans, and LPS) and increase Toll-like Receptor (TLR)-2 and TLR-4 signaling to amplify the host immune response and inflammation causing collateral damage to periodontal tissues (Darveau, 2010; Degasperi et al., 2018).

3 | CELLULAR SIGNALING PATHWAYS IN INFLAMMATION

Cytokines and chemokines are low molecular weight proteins that act as messengers between and within cells (Turner, Nedjai, Hurst, & Pennington, 2014). Depending on the cell type, location, and microenvironment, cytokines and chemokines have specific roles in increasing or decreasing the host immune response; cytokines such as IL-6 have dual roles and can act as either pro- or anti-inflammatory signals (Degasperi et al., 2018). Once cells recognize bacteria via PAMPs, TLRs typically signal through a myeloid differentiation primary response 88 (MyD88) dependent pathway which leads to nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation and translocation to the nucleus, where it increases the transcription of proinflammatory cytokines TNF-α, IL-1β, prostaglandin E-2 (PGE2), and IL-6 (Nagao et al., 2017). LPS and calprotectin can also act as a proinflammatory ligand for TLR-4 and receptor for advanced glycation end products acting to increase mRNA and protein expression of IL-6 and receptor activator of nuclear factor kappa-B ligand (RANKL) (Nagao et al., 2017). Calprotectin is another protein capable of increasing IL-6, IL-8, and TNF-α in periodontal ligament fibroblasts (Naruishi & Nagata, 2018; Nishikawa et al., 2017). TNF-α also increases production of IL-1β and IL-6 to promote degradation of the extracellular matrix and increase RANKL production. RANKL then binds with receptor activator of nuclear factor kappa-B (RANK) on osteoclast precursor cells, inducing osteoclast differentiation and maturation leading to increased bone resorption (Batool et al., 2018). Of the interleukins, IL-1 and IL-6 families of cytokines play especially important roles in the pathogenesis of periodontal disease and many other inflammatory diseases (see Table 1). In brief, IL-1 signals through receptors (IL-1R) which share functional Toll/Il-1 Receptor (TIR) domains with the TLRs. The conserved TIR in both receptors induces cyclooxygenase-2, proinflammatory cytokines, and other cell signals in identical manners. IL-1R3 acts as a coreceptor with IL-1R1 and forms a heterotrimer with either IL-1α or IL-1β which then binds MyD88 and causes a kinase cascade, strong NFκB signaling, and an increase in inflammation which damages surrounding tissues (Dinarello, 2018a).

Resolution of periodontal disease and inflammation is an active process that requires many opposing signals to downregulate inflammatory cytokines, prevent immune cell trafficking, and increase immune cell apoptosis and clearance (Darveau, 2010). Anti-inflammatory cytokines (such as IL-10 and IL-6 in the right environment) inhibit the synthesis of proinflammatory cytokines IL-1, TNF-α, and increase Th2 cell production of anti-inflammatory signals (Bostanci et al., 2017). A return to health is achieved when inflammation is resolved, pathogenic bacteria are under control, and commensal bacteria have recolonized the sulcus returning the host-microbe balance to homeostasis (Darveau, 2010).

Pathogenic bacteria have developed unique methods to subvert the host immune response (Darveau, 2010). *Fusobacterium nucleatum* utilizes an ABC transporter permease gene for resistance to multiple drugs (Herrero et al., 2018). *P. gingivalis* induces IL-8 paralysis in epithelial cells, preventing neutrophil trafficking to the site of infection. If cells escape IL-8 paralysis from *P. gingivalis*, *Treponema denticola* possesses an outer membrane capable of degrading IL-8 to prevent chemokine signaling to neutrophils (Degasperi et al., 2018). *P. gingivalis* also pairs with C-X-C Motif Chemokine Receptor (CXCR)-4 to dampen TLR signaling and avoid the antibacterial actions of inflammation and can degrade proinflammatory cytokines while invading host cells to effectively hide until the proinflammatory response has abated (Darveau, 2010; Ramage et al., 2017). Lipid A, found in most Gm− bacteria, acts as a TLR-4 antagonist limiting mitogen-activated protein kinase and extracellular signal-regulated kinase signaling and preventing downstream production of proinflammatory cytokines (Darveau, 2010). *P. gingivalis* induces IL-17 secretion in immune cells

which drives Th17 differentiation of T cells and stimulates osteoclastogenesis via cooperation with Th1 responses and a significant increase in RANKL expression (Degasperi et al., 2018). *Prevotella intermedia* is capable of degrading neutrophil extracellular traps to protect bacteria in biofilm from destruction (Degasperi et al., 2018).

4 | CHAIRSIDE DIAGNOSTIC TESTING

Inflammation and the oral microbiome can have a significant impact on systemic health and the exacerbation of other inflammatory diseases. However, with over 700 species of bacteria able to colonize the oral cavity, with several of those yet to be successfully cultured for bench research, there needs to be a renewed focus on controlling inflammation rather than infection (Berezow & Darveau, 2011; Darveau, 2010; Van Dyke, 2017). Chairside diagnostics can be used to bridge gaps between oral and systemic health care with an aim of improving whole patient health. On a cellular level, there are many inflammatory markers which could be used to determine disease severity or resolution post-treatment. Assessing a patient's health and dental histories is a good starting place to determine which diagnostics are most important. For example, gastroesophageal reflux disease has been shown to follow the same Gm+ to Gm− dysbiosis pattern as periodontal disease (Berezow & Darveau, 2011; Darveau, 2010); therefore, evaluating a patient who presents with gastrointestinal pain along with persistent oral inflammation for levels of LPS and LTA could potentially help dentists and physicians diagnose the underlying causes of both disorders. Calprotectin is another molecule which has a large impact on the progression of systemic inflammatory conditions and acts as a marker of periodontal disease severity (Nishikawa et al., 2017). Periodontally located IL-6 signaling can induce Th1 and Th17 cytokines leading to production of C-reactive proteins independent of hepatic production (Hernandez-Caldera et al., 2018). IL-6 has been shown to be positively correlated with periodontal disease severity and severity of rheumatoid arthritis (Silvestre-Rangil, Bagan, Silvestre, Martinez-Herrera, & Bagán, 2017). Many cytokines consistently have been shown to increase in cases of periodontal disease and decrease following initial periodontal therapy (IPT) and a return to clinical gingival health. IL-1β, IL-1α, and IL-6 are all critical mediators of periodontal inflammation and can be measured in gingival crevicular fluid, serum, and saliva in levels corresponding to the clinical severity of the disease (Abdolsamadi, Vahedi, Esmaeili, Nazari, & Abdollahzadeh, 2008; Batool et al., 2018; Bostanci et al., 2017; Reis et al., 2014; Zekeridou, Giannopoulou, Cancela, Courvoisier, & Mombelli, 2017). IL-6 specifically shows a marked increase during disease, with a significant downregulation after treatment with IPT (Bostanci et al., 2017; Silvestre-Rangil et al., 2017; Zhang, Huang, Lu, Zhang, & Cai, 2016). While determining site-specific identifiers of disease may not be practical, assessing the overall inflammatory state of the periodontium could be crucial in cases of refractory periodontitis of unknown etiology (Zekeridou et al., 2017). Salivary diagnostics are an easy and non-invasive way to assess levels of inflammatory marker expression (Nagarajan, Miller, Dawson, Al-Sabbagh, & Ebersole, 2015). Utilizing a panel of diagnostic markers, as opposed to a single classifier (i.e., IL-6 and IL-1β, compared to IL-6 alone), allows researchers and clinicians the ability to demonstrate individual variations and subsets of patients with alternate expressions within broader groups of health, gingivitis, or periodontitis (Nagarajan et al., 2015). Use of cumulative risk scores including levels of periodontal pathogen burden (*P. gingivalis*), inflammation (IL-1β), and bone destruction (MMP-8), as determined by a combination of immunoassays and polymerase chain reaction tests, is another method to evaluate a person's overall oral health status, not limited by a single specific diagnostic marker. While cumulative risk analysis is not yet available for commercial or point-of-care use, it shows promise for future application (Gursoy et al., 2011; Gursoy, Pussinen, Salomaa, Syrjalainen, & Kononen, 2018). A broader understanding of unique patient expression levels would allow clinicians to identify the expression profile unique to each individual and to assess changes in expression levels as diagnostic, or potentially prognostic, indicators of disease progression or response to treatment (Nagarajan et al., 2015).

While not the focus of this manuscript, it should be noted that MMP-8, also known as neutrophil collagenase, was shown to be an important marker in assessing the status and progression of periodontal disease (Sorsa, Gieselmann, Arweiler, & Hernández, 2017). MMP-8 is a collagenase which is partially responsible for the tissue destruction seen in periodontal disease and can be found reliably in gingival crevicular fluid samples and saliva of patients with active periodontitis (Sorsa et al., 2017). Commercially available point-of-care diagnostics in the form of oral fluid tests achieve high sensitivity (76%–83%) and specificity (96%) in multiple independent analyses (Alassiri et al., 2018; Al-Majid et al., 2018; Heikkinen et al., 2016, 2017; Leppilahti et al., 2018; Sorsa et al., 2016).

5 | CHAIRSIDE DIAGNOSTICS: GENETIC MUTATIONS

Along with inflammatory signaling molecules, genetic mutations are also an emerging diagnostic tool. Single nucleotide polymorphisms (SNPs) are mutations where one nucleotide in the amino acid sequence is switched for another. SNPs can affect the shape of the DNA structure and modify the gene's active binding site causing a deviation in downstream transcription and translation abilities. In a 2017 meta-analysis, it was determined that polymorphisms in the genes encoding IL-1α, IL-1β, IL-6, IL-10, MMP-3, and MMP-9 were all significantly associated with an increased risk of developing periodontitis (da Silva et al., 2017). Another 2017 study showed the specific SNPs of IL-6(-174) and IL-10(-597) were associated with the development of generalized aggressive periodontitis (Bostanci et al., 2017). Yet another study in 2018 demonstrated SNPs of

IL-10(rs1800872 (-592A)) corresponded with an increase in bleeding on probing and risk of further disease progression (Chatzopoulos, Doufexi, Wolff, & Kouvatsi, 2018). The study showed no correlation between SNPs of IL-6(rs1800796(-572G)) and any increase in disease severity, even though the mutation was accompanied by increased protein expression (Chatzopoulos et al., 2018). Additionally, there are genetic variations within an individual, such as DNA hypomethylation, which can modify the host response to pathogens, thereby potentially altering a person's risk of disease development in specific sites (Kobayashi, Ishida, & Yoshie, 2016).

6 | CHAIRSIDE DIAGNOSTICS: INTERPRETATION AND CLINICAL IMPLICATION

While there are a host of genetic factors influencing the onset and progression of periodontal disease, two of the most common targets for chairside diagnostics are mutations in the genes encoding the proinflammatory cytokines IL-1 and IL-6. Table 2 is an example of the report returned to oral health providers after submitting a sample for DNA analysis (Oral DNA Labs, 2016, 2017a, 2017b). Yet what do these results mean to the clinician or to the patient? Should clinicians change treatment modalities for periodontitis based on the results of chairside diagnostics tests or host genetic factors? If so, how? In our example chart (Table 2), the patient has low-risk variants of β-defensin-1 and CD14, so inflammatory pathways utilizing those molecules would not be expected to increase in response to bacterial load. The patient's TNF-α genotype possibly increases the risk of proinflammatory signaling pathways as a result of bacterial load, and the high-risk alleles seen for IL-1α, IL-1β (Sometimes seen as IL-1A or IL-1B), and IL-6 indicate a likely significant increase in inflammation and tissue destruction despite lower levels of bacteria (Oral DNA Labs, 2016, 2017a, 2017b). An increased reaction to bacterial colonization could potentially place the individual at an increased risk of systemic inflammatory conditions, especially in the presence of other concomitant factors such as smoking or family history of disease. Genetic information is only one aspect of periodontal disease pathogenesis and should be used in conjunction with all clinical and health history findings to determine the overall diagnosis and prognosis for an individual. Oral health care providers can use this information to reinforce the patient's need for improved homecare efforts or to explain in part why the patient might be more susceptible to disease than his or her peers. Most reports will provide additional information regarding the fold-increase of disease progression and specific SNP mutation and location for the given individual (Oral DNA Labs, 2016, 2017a, 2017b). While the reports can help guide conversations about diagnosis, prognosis, and therapeutic options, the information must be kept in context as only one small portion of the individual's overall risk assessment and treatment planning (Oral DNA Labs, 2016, 2017a, 2017b).

TABLE 2 Example of genetic testing final report

Marker	Genotype	Risk
β-defensin 1	G/A	Low
CD14	T/T	Low
TNF-α	C/C	Intermediate
IL-1α	C/T	High
IL-1β	T/T	High
IL-6	G/G	High
Sources	OralDNALabs, 2017A; OralDNALabs, 2017B; OralDNALabs, 2016	

7 | CURRENT ISSUES IN CHAIRSIDE DIAGNOSTICS

While the future of chairside diagnostics is incredibly promising, there is still much work to be done before chairside diagnostics can become the standard of care for periodontal patients. Current technology allows researchers and dental practitioners to evaluate inflammatory biomarker expression in individuals using saliva, gingival crevicular fluid, or serum; however, longitudinal studies need to be conducted to accurately determine which markers can be used in risk assessment and prognosis of disease progression (Nagarajan et al., 2015). A deeper understanding of the vast mechanisms involved in periodontal disease pathogenesis, inflammation, and the link between oral and systemic inflammation will help focus the development of new technologies to be used for personalized care. Further exploration of genetic SNPs and mutations in patients across all diagnostic categories will aid in understanding the differences between patients. As with all technological advances, cost and standardization of use are hurdles that need to be overcome for the science of chairside diagnostics to be utilized as the standard of care.

8 | DISCUSSION

The future of predictable, personalized, and preventative precision dentistry and evidence-based decision making will incorporate the use of chairside testing for inflammatory biomarkers and genetic mutations as a method of disease diagnosis and prognosis (Nagarajan et al., 2015). Dental professionals will be able to detect individuals transitioning from health to gingivitis, or from gingivitis to periodontitis, instead of waiting for the immune response to cause clinically visible damage prior to initiating treatment (Nagarajan et al., 2015). In order to fully utilize the current and future diagnostic aids, dental practitioners must understand the pathophysiological basis of detecting specific molecules, and the subclinical impact those markers have on inflammation. While many more studies need to be done to discern the appropriate panels for diagnostic, prognostic, and oral/

systemic associated disorders, the premise of tailoring treatment to a unique individual, rather than to a broad group of patients, is extraordinary.

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AUTHOR CONTRIBUTIONS

Courtney Rudick completed the literature review, wrote the manuscript, and made suggested revisions. Dr. Melissa Lang provided expert guidance and revisions for the manuscript. Dr. Takanari Miyamoto determined the review topic, provided expert guidance and revisions for the manuscript.

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