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An appraisal of the role of specific bacteria in the initial pathogenesis of periodontitis

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Abstract

Background: Historically, inflammatory periodontal diseases (gingivitis and periodontitis) have been recognized as being primarily of bacterial origin. Bacteria are necessary for disease development, but the presence of specific bacteria does not guarantee progression to periodontitis. Periodontitis is a multifactorial disease; specific bacteria are associated with disease, but may not be the target of treatment. Gingivitis and periodontitis are inflammatory conditions associated with bacterial overgrowth.

Aim: To analyse evidence for established thought that *specific* bacteria directly participate in the pathogenesis of periodontitis and question the long-held tenet that penetration of the periodontal connective tissues by bacteria and their products is a significant phase in the initial development of periodontitis.

Methods: The literature was searched for studies on initiation of gingivitis and periodontitis by specific pathogens. The search results were insufficient for a systematic review and have been summarized in a commentary instead.

Results: There is very little evidence in the literature to support the commonly held concept that specific bacteria initiate periodontitis.

Conclusion: We present evidence for a paradigm supporting the central role of inflammation, rather than specific microbiota, in the early pathogenesis of periodontitis, and discuss whether controlling the inflammation can influence the character and composition of the periodontal infection.

Keywords

periodontal infection; periodontal inflammation; periodontal pathogen; bacterial invasion; gingivitis; periodontitis

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Dr. Van Dyke is named in patents held by the Forsyth Institute that are subject to potential royalties or consulting fees.
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Introduction

Periodontitis, an inflammatory condition associated with bacterial infection, is modified by multiple host response genes in combination with lifestyle and environmental factors (Bartold and Van Dyke, 2013). The search for the causative periodontal pathogen(s) continues; however, emerging evidence suggests that it is the inflammatory response that drives changes in the periodontal microbiome and amplifies pathogenesis of progressive periodontitis.

Infection, Inflammation and Tissue Destruction

Plaque deposits account for only 20% of the risk for periodontitis (Grossi et al., 1994). Factors that contribute to the remaining 80% include environmental determinants and individual genetic variation that modify inflammation and its resolution (Kornman, 2008). Importantly, anti-infective therapy alone fails to effectively manage as many as 25% of periodontitis patients (Kornman et al., 2017). Most individuals with poor oral hygiene and little or no periodontal care develop only mild/moderate periodontitis (Loe et al., 1986, Baelum et al., 1986). The individual, not bacterial composition, determines risk for disease and adverse treatment outcomes (Socransky and Haffajee, 2005).

Hypotheses for the Development of Periodontitis

The ecological plaque hypothesis (Marsh, 1994), the keystone pathogen hypothesis (Hajishengallis et al., 2012, Hajishengallis and Lamont, 2012) and the polymicrobial synergy and dysbiosis model (Lamont and Hajishengallis, 2015) have widespread acceptance in contemporary periodontology. These hypotheses are consistent with observed reciprocal interactions between complexes of bacteria whereby gingival inflammation, in response to early colonising bacteria, changes the subgingival environment allowing increases in certain endogenous commensal bacteria (Socransky and Haffajee, 2002; Socransky and Haffajee, 2005).

However, these models fail to fully explain host-microbe interactions in health and disease. All three hypotheses place considerable emphasis on specific (keystone) bacteria being the driving force behind the development of periodontitis. While intuitively sound, the evidence is not conclusive. The oral microbiome in health is symbiotic (Dongari-Bagtzoglou, 2008). Putative pathogens are present in health, but are not pathogenic (Kolenbrander et al., 2010). We recognize that periodontitis is a continuum of inflammation, tissue destruction and microbial dysbiosis modified by factors such as smoking, systemic diseases and genetics. Further investigations into these complex interactions must determine how the metagenome of the host and microbes interact to result in disease.

Are specific bacteria the cause of periodontitis?

Early studies identified *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Tannerella forsythia* as “periodontal pathogens” (American Academy of Periodontology, 1996). The subgingival microbiota from periodontal health to periodontitis demonstrates ecologic succession, with emergence of dominant taxa in periodontitis without replacement of health-associated species (Oliveira et al., 2016), and an increase in bacterial load.

Recently, an additional 13 periodontal pathogens were identified (Oliveira et al., 2016). While these bacteria are present, we cannot infer that they cause periodontitis. It is just as likely they are selected for by inflammation-mediated environmental changes. To find "causative" periodontal pathogens, temporal data are required.

Can systemic inflammation modify periodontal destruction?

While not proven in humans, evidence from animal models shows that systemic inflammation results in exacerbation of periodontal inflammation and destruction. In three independent studies, induction of experimental arthritis had adverse actions on the periodontium in the absence of induction of experimental periodontitis (Ramamurthy et al., 2005; Park et al., 2010; Cantley et al., 2011).

Is bacterial invasion of the periodontal tissues an initiating event in periodontitis?

Penetration of periodontal tissues by bacteria and/or their metabolic products has long been considered a crucial step in the pathogenesis of periodontitis (Ji et al., 2015). However, this plausible assumption is based on very little supporting *in vivo* or *in situ* evidence. While studies report the presence of bacteria, or their products, in periodontal tissues (Ji et al., 2015), most, if not all, used biopsies from advanced periodontitis lesions (Guyodo et al., 2012, Kim et al., 2010, Baek et al., 2018). There are no publications concerning bacterial permeation in healthy, gingivitis or early periodontitis tissues. Invasion of epithelial cells by periodontal bacteria is reported *in vitro*, but *in vivo* demonstration has been limited (Tribble and Lamont, 2010). Furthermore, bacterial migration from within gingival epithelial cells across an intact basement membrane and into the gingival connective tissue has not been demonstrated *in vivo*. While bacterial/dendritic cell interaction has been demonstrated, this is confined to dendritic cells in the epithelium, not the underlying connective tissue (Cutler et al., 1999, Jotwani et al., 2001; El-Awady et al., 2015). No *in vivo* evidence exists for interaction/interface between fibroblasts, osteoblasts or osteoclasts and invading bacteria. In very advanced periodontitis, bacteria may be found in close approximation to CD-4 positive T cells (Guyodo et al., 2012).

What happens during the initial stages of development of the periodontal diseases?

It is essential to understand what happens at the during initiation of disease followed by definition of ensuing events. Several key factors should be considered:

1. **Sulcular Epithelium: Barrier function and antimicrobial peptides—**The epithelium provides a physical barrier between the external and internal environments (Bartold et al., 2000). In addition, the sulcular epithelium, in response to the accumulating bacterial load, releases potent antimicrobial peptides (alpha- and beta-defensins), as well as chemokines and cytokines responsible for neutrophil recruitment (Dale, 2002, Chung et al., 2007). Phagocytosis of bacteria and formation of a cellular barrier between the subgingival plaque and the epithelium ensues (Schroeder & Attstrom, 1980; Kornman et al., 1997). Given the critical role of innate immunity associated with the epithelium, it is time to consider the role periodontal epithelium plays in maintaining health and alerting the host of bacterial assault.

2. **Epithelial Shedding and Epithelial cell renewal—**The continuous shedding, turnover and replacement of gingival epithelial cells protects against invading bacteria. Non-keratinized tissues of the gingival sulcus have a 50% higher mitotic rate than the keratinized regions of attached gingiva that is increased in the presence of inflammation of the underlying connective tissue (Soni et al., 1965).

3. **Gingival Crevicular Fluid—**Gingival crevicular fluid (GCF) flow approximates 20 μL/h and increases dramatically with gingival inflammation. In a 5 mm pocket GCF is replaced 40 times/hour (Goodson, 2003). During transition from health to disease, GCF changes in composition, pH, oxygen levels, temperature, osmotic pressure and redox potential. Importantly, the rise in pH together with a rich source of nutrients from ongoing tissue destruction and bacterial metabolic activity favours the proliferation of acid-sensitive "pathogenic" bacteria (Barros et al., 2016).

4. **Initial inflammatory response—**Initially, the host contains the subgingival infection and tissue damage is limited to gingivitis with no ingress of specific bacteria or their metabolic products. If the inflammation cannot be resolved, the inflammatory exudate increases and alters the pocket environment allowing commensal bacteria, including *P. gingivalis*, to overgrow. The subgingival microbiome develops a disease-associated "dysbiotic" relationship dictated primarily by inflammation. With continuing bacterial challenge and uncontrolled gingival inflammation, the epithelial barrier is breached and new environment develops. It is conceivable that at this stage bacterial penetration of the tissues could occur. Continued inflammation leads to loss of periodontal ligament fibers, clinical loss of attachment and deepening of the periodontal pocket. Importantly, bone resorption is not directly microbial-induced; activation of osteoclasts is stimulated by inflammatory mediators.

Is there evidence in other systems for inflammation-mediated dysbiosis?

Dysbiosis, first described over 100 years ago in the gut, described disrupted symbiosis between bacteria and host (Plotnikoff and Riley, 2014). Dysbiosis of the gut is a useful model for understanding periodontal dysbiosis because, like periodontal dysbiosis, it is directly related to inflammation or immunodeficiency (Lupp et al., 2007, Kamada et al., 2013). It has been proposed that controlling gut inflammation is a good approach to limiting blooms of disease-associated bacteria (Zeng et al., 2017). Thus, evidence in other systems supports that it is inflammation that drives development of dysbiosis.

An inverted model for the pathogenesis of Periodontitis - inflammation exacerbates infection

The initial inflammatory response in periodontal disease(s) always precedes the emergence/overgrowth of periodontal pathogens (Lindhe et al., 1980, Listgarten, 1988, Tanner et al., 2007). Accordingly, an "inverted paradigm" is proposed whereby increasing inflammation selects specific bacteria based on growth requirements. Once overgrown, these bacteria promote inflammation to maintain their selective dominance (Figure 1).

Management of periodontitis can be based on controlling the inflammation to control the infection (Bartold and Van Dyke, 2013, Bartold and Van Dyke, 2017). This inverted paradigm, which has been demonstrated experimentally in animal models (Hasturk et al. 2007, Lee et al. 2016), must be applied in the context of understanding that the ultimate successful clinical outcome of periodontal treatment will result from controlling, or resolving, the inflammatory response.

Future Research Directions

- **Consider the validity of in vitro studies—**There are innumerable examples of *in vitro* observations that are not reproducible *in vivo*. For example, direct interactions of bacteria with periodontal fibroblasts, bone cells, PMNs or lymphocytes are not supported by histopathological evidence. Studying such interactions *in* vitro is not warranted without *in vivo* confirmation.

- **Investigate the continuum of disease—**Descriptive studies of the progression of health to advanced periodontitis were performed in the 1970s. Mechanistic studies of the continuum are required.

- **Modulate inflammation to modulate periodontal infection—**Effective host response modulation is a crucial element missing in our current armamentarium of conventional periodontal therapy. Targeting inflammation reverses periodontitis and dysbiosis in animals. Studies are required in humans with active agents, not inhibitors of inflammation.

Conclusions

Current paradigms of initiation of periodontitis require reassessment. Traditional plaque control management approaches are only partially effective for periodontitis and fail in high-risk individuals. More detailed consideration of the host response, genetic and environmental factors is required. While the possibility exists that a hitherto unknown bacterial species may one day be identified as a true pathogen, this has eluded researchers for decades. Concepts focused on controlling the infection to control the inflammation should be reworked to consider controlling the inflammation to control the infection.

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Clinical Relevance:

Scientific Rationale.

Understanding disease pathogenesis requires knowing what initiates the disease followed by definition of ensuing events. There has been an overemphasis on the role of *specific* bacteria in the initiation of periodontitis at the expense of considering the host response, genetic and environmental factors.

Principle Findings.

The etiology of periodontitis is bacteria. However, evidence points to the pathogenesis being inflammatory. Data supporting *in vivo* invasion by bacteria has not been convincingly demonstrated; putative pathogens are part of the normal flora and overgrow after onset of disease, which is reversible by controlling inflammation; the 'keystone pathogen' hypothesis has no *in vivo* or *in vitro* evidence to support it; direct interactions of bacteria with fibroblasts or osteocytes is not supported by histopathological evidence.

Practical Implications.

Concepts focused solely on controlling the infection to control the inflammation should be reworked to consider controlling the inflammation to control the infection.

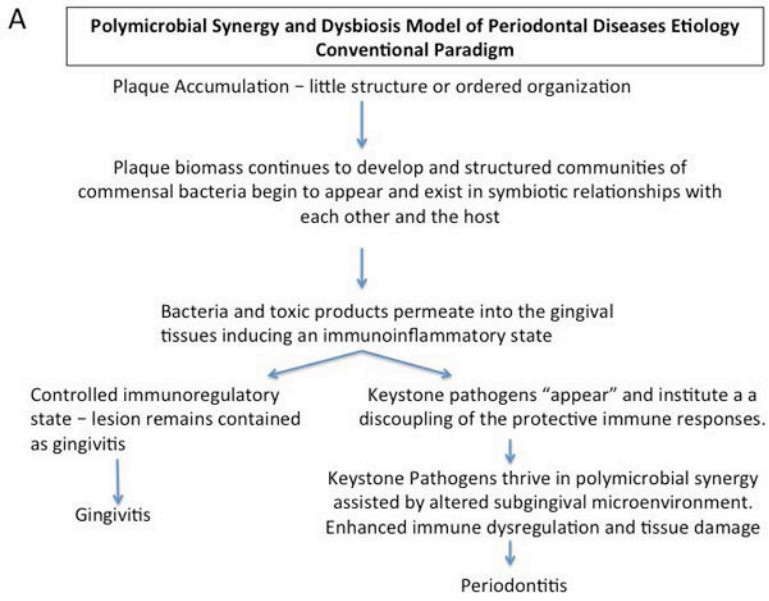

Figure 1a.

Conventional paradigm of polymicrobial synergy and dysbiosis model as a hypothesis for the pathogenesis of periodontitis

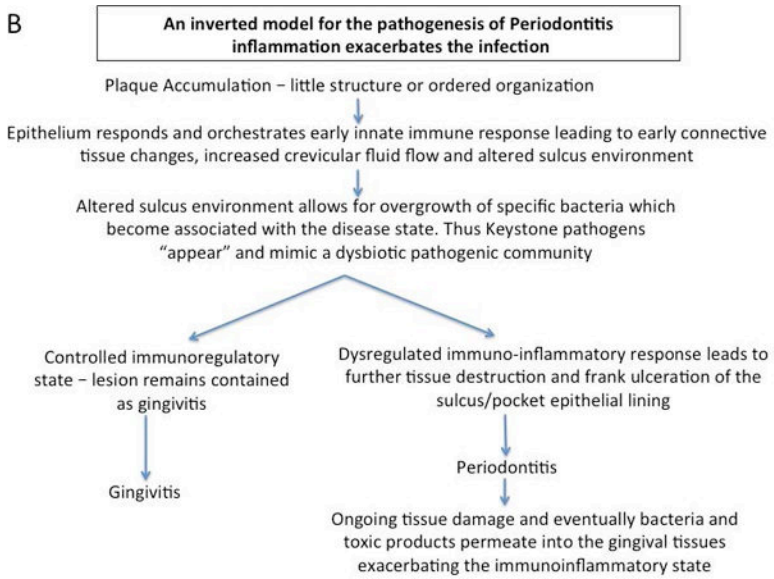

Figure 1b.

Inverted paradigm hypothesis for the pathogenesis of periodontitis whereby inflammation drives and exacerbated periodontal infection