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How is the development of dental biofilms influenced by the host?

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Abstract

Background: The host provides environmental conditions that support diverse communities of microorganisms on all environmentally-exposed surfaces of the body.

Materials and Methods: To review the literature to determine which properties of the host substantially influence the development of dental biofilms.

Results: The mouth facilitates the growth of a characteristic resident microbiota. The composition of the oral microbiota is influenced by temperature, pH, and atmosphere, as well as by the host defences and host genetics. In addition, the host supplies endogenous nutrients and a variety of surfaces for biofilm formation. In health, the resident oral microbiota forms a symbiotic relationship with the host, regulated by active host–microbe cross talk. This resident microbiota is sensitive to perturbations in the host environment, especially to changes in nutrient supply and pH, so that previously minor components of the microbiota can become more competitive (and *vice versa*), resulting in reorganization of biofilm community structure.

Conclusion: The host environment dictates the composition and gene expression of the resident microbiota. Changes in oral environmental conditions can disrupt the normal symbiotic relationship between the host and its resident microbes, and increase the risk of disease.

Key words: biofilm; dental plaque; ecology; interventions; periodontal disease

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Humans have not evolved independently of other life forms; in particular, they have an intimate and dynamic relationship both with the microorganisms that make up the resident microbiota of all environmentally exposed surfaces of the body as well as those that cause disease. The human body is estimated to be composed of more than 10^{14} cells, of which only 10% are mammalian. The majority are the microorganisms that colonize the skin, mouth, digestive, and reproductive tracts (Wilson 2005). These microbiotas are distinct from each other despite the frequent transfer of organisms between these sites; their characteristic composition is due to significant differences in the biological and physical properties of each habitat. This observation illustrates a key concept; namely, that the properties of the habitat are selective and dictate which organisms are able to colonize, grow, and become minor or major members of a microbial community.

The resident human microbiota does not merely reside passively at a site, but makes an active contribution to the maintenance of health by promoting the normal development of the physiology of the host (including the immune system), and by excluding exogenous (and often pathogenic) microorganisms (colonization resistance) (Wilks 2007). In general, the host lives in a relatively stable and harmonious relationship with its resident microbes (termed microbial homoeostasis), and both parties benefit from this symbiosis (Marsh 1989). However, if this homoeostasis breaks down, then the dynamic nature of the host–microbe relationship can result in either exogenous microorganisms being able to colonize, or previously minor components of the resident microbiota exploiting new opportunities and increasing in proportion, which in certain circumstances can pre-dispose the site to disease.

Oral microbial ecology is focussed on understanding the interactions that occur between the microbes that inhabit the mouth and the host that supports their existence. In order to understand the relationship between the oral microbiota and the host in health and disease, and to develop more effective interventions, it is essential to appreciate the ecological concepts that underpin and define these interactions. Consequently, this review will explore current knowledge on how the properties of the host can influence the development of dental biofilms.

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The Mouth as a Microbial Habitat

The mouth provides a warm and moist environment that suits the growth of many microorganisms. The mouth is

the only site in the human body that normally provides non-shedding surfaces for microbial colonization; this facilitates the development of thick biofilms, particularly at stagnant sites whereas desquamation ensures that the microbial load is lighter elsewhere. Thus, in this way, the host provides unique opportunities for biofilm formation in the mouth, and a secure haven for microbial persistence (Socransky & Haffajee 2002, Marsh et al. 2005, 2010).

The composition of the oral microbiota varies significantly at distinct surfaces within the mouth such as the tongue, buccal mucosa, and teeth (Aas et al. 2005, Zaura et al. 2009, Dewhirst et al. 2010). This simple observation re-inforces the important ecological principle that differences in key environmental conditions that prevail at particular oral sites will determine which organisms will be most competitive and predominate. This observation also illustrates that the properties of the host habitat dictate which organisms will be able to colonize, grow, and be minor or major members of the microbiota and that the microbes that inhabit these sites are sensitive and responsive to the host environment they inhabit.

The mouth is also hostile to microbial life, and so only a subset of the microbes that enter the oral cavity are able to colonize and survive. Microorganisms have to attach to a surface and form biofilms in order to persist. Microbial inhabitants have to develop strategies to cope with the innate and adaptive arms of the host defences (Marsh & Martin 2009). Once organisms have colonized, nutrients must be acquired in order for growth and cell division to occur, and species have to compete with other resident microbes in order to become established. Clearly, given the richness of the resident oral microflora, many species have adapted successfully to these conditions (Zaura et al. 2009, Dewhirst et al. 2010).

Properties of the Host Environment that Influences Microbial Growth

The fact that certain microorganisms are consistently isolated from a habitat indicates that all of their growth requirements such as nutrition, atmosphere, pH, and redox potential are being met. Environmental conditions vary at different sites in the mouth and at a surface during the transition from health to disease. Microorganisms respond to such changes in the environment and alter their pattern of gene expression in order to adapt. Particular emphasis will be put on factors that can shift the composition and metabolism of the subgingival microbiota in a way that would promote the likelihood of tissue damage (Fig. 1).

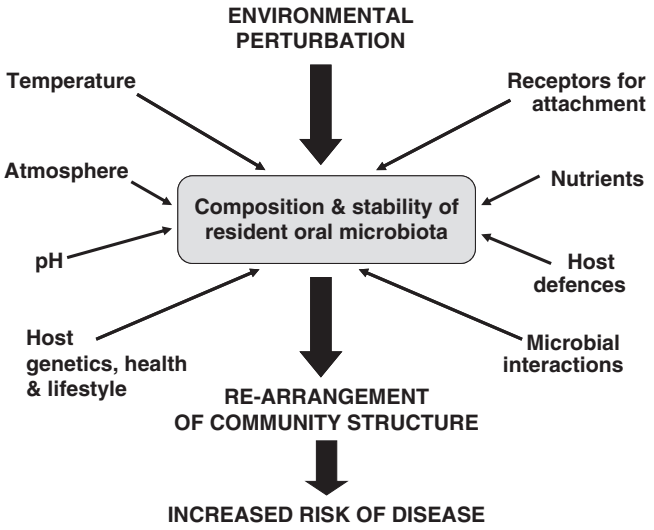

Fig. 1. Host factors that influence the microbial composition, activity, and stability of the resident oral microbiota. A perturbation in a key environmental factor can disrupt the natural stability of the resident microbiota (microbial homeostasis) at a site and result in a re-arrangement of the composition and activity of the resident microbial community; such a change might pre-dispose the site to disease.

Temperature and redox potential

The local temperature will increase with inflammation, and differences of over 2°C between periodontally healthy and diseased sites have been measured (Fedi & Killoy 1992). A small rise in temperature may alter the ecology of a site by altering the competitiveness of organisms. Subgingival sites with higher temperatures had elevated proportions of *Prevotella intermedia*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis* (Haffajee et al. 1992). The small changes in temperature at inflamed subgingival sites can significantly alter bacterial gene expression. A rise in temperature to 39–41°C down-regulated expression of proteases of *P. gingivalis* as well as the gene coding for the major subunit protein of fimbriae that mediates attachment of the bacterium to host cells (Amano et al. 1994, Percival et al. 1999, Murakami et al. 2004). In contrast, an increase in temperature up-regulated the synthesis of superoxide dismutase (Amano et al. 1994).

The distribution of anaerobes in the mouth is related to the redox potential at a site, although some survive at overtly aerobic habitats by existing in close partnership with oxygen-consuming species. Bacterial metabolism in mature oral biofilms results in gradients of oxygen and Eh and so the host provides an environment suitable for the growth of bacteria with a range of oxygen tolerances. Part of the host defence systems for oral tissues involves production of free radicals and reactive oxygen species, which will restrict or prevent microbial growth.

pH

Most oral microorganisms require a pH around neutrality for optimal growth, and are sensitive to extremes of acid or alkali. The pH of most surfaces of the mouth is regulated by saliva that has a pH in the range 6.75–7.25. Changes in environmental pH can cause major shifts in the proportions of bacteria within dental plaque biofilms. After sugar consumption, the pH in plaque can fall rapidly to below pH 5.0 by the production of acidic fermentation products (Marsh & Martin 2009). Depending on the frequency of sugar intake, the bacteria in plaque will be exposed to varying challenges of low pH. Many of the predominant plaque bacteria that are associated with healthy sites can tolerate brief conditions of low pH, but are inhibited or killed by more frequent or prolonged exposures to acidic conditions (Svensater et al. 1997). This can

result in the enrichment of acid-tolerant (aciduric) species, especially mutans streptococci and lactobacilli, which are normally absent or only minor components in dental plaque at healthy sites. Such shifts in the bacterial composition of plaque pre-dispose a surface to dental caries (Fig. 1).

The pH of the healthy gingival crevice is approximately 6.9, but this rises to between pH 7.2 and 7.4 following inflammation, with a few patients having pockets with a mean pH of around 7.8 (Eggert et al. 1991). This rise in pH is probably a result of an increase in proteolytic bacterial metabolism, e.g. ammonia production from urea and from the deamination of amino acids. Even a small change in pH can alter the growth rate and pattern of gene expression in subgingival bacteria, for example, the expression of proteases by *P. gingivalis* increases at alkaline pH, and thereby can increase the competitiveness of some of the putative pathogens (McDermid et al. 1988, Marsh et al. 1993). This could favour the growth of periodontal pathogens, such as *P. intermedia*, *P. gingivalis*, and *A. actinomycetemcomitans* that have alkaline pH optima for growth (McKee et al 1984, Hamilton et al. 1989, Sreenivasan et al. 1993).

Nutrients

Microorganisms that make up the resident microbiota of a site are dependent on the host habitat for the nutrients essential for their growth. Therefore, the association of an organism with a particular habitat is direct evidence that all of the necessary growth-requiring nutrients are present. Nutrients such as amino acids, proteins, and glycoproteins are obtained from endogenous supplies, and mainly from saliva, although gingival crevicular fluid (GCF) is another potential source. The low flow of GCF in health means that it makes a minor contribution to the growth of the normal subgingival microbiota. Saliva contains amino acids, peptides, proteins, and glycoproteins (which also act as a source of sugars and amino-sugars), vitamins and gases, and it also provides the main buffering capacity for the mouth (Marsh & Martin 2009). The catabolism of the more complex host molecules, such as host glycoproteins, requires the sequential or concerted action of consortia of bacteria, in which their metabolic capabilities are combined (ter Steeg & van der Hoeven 1989, Bradshaw et al. 1994, Wickstrom et al. 2009). Importantly for the stability of the microbial consortium, the metabolism of these substrates leads to only minor and slow changes to the local pH, which are well tolerated by the normal resident microbiota. In contrast, and as described in the section above, the main impact of diet is the provision of fermentable carbohydrates that leads to ecologically devastating falls in pH, which if repeated frequently enough, lead to the selection of acidogenic and acid-tolerating bacteria (Bradshaw et al. 1989), and a greater risk of dental caries.

Host genetics and ethnicity

A relatively poorly understood parameter is the influence of the genetics of the host on the composition of the resident oral microbiota (Rylev & Kilian 2008). Studies of periodontal disease have suggested that host genetics and ethnicity can influence disease susceptibility, and possibly also affect the microbiota. Genetic polymorphisms associated with interleukin (IL)-1, or other cytokines, can increase the likelihood of detecting certain key periodontal pathogens, and pre-dispose individuals to periodontitis (Socransky et al. 2000). A wide selection of strains of *A. actinomycetemcomitans* have been isolated from different geographical areas and screened for their genetic relatedness. One clone was found to over-produce a leukotoxin, and isolates came from individuals who could be traced to north-west Africa, suggesting a potentially specific host tropism (see Haubek 2010). In patients with periodontitis, *P. gingivalis* and *Peptostreptococcus anaerobius* were associated more with African American subjects whereas *Fusobacterium nucleatum* was found more commonly in Caucasian individuals. This possible relationship with ethnicity can be complex; however, as highlighted by a study of younger, healthy subjects living in California. There was a trend of an increased likelihood of detecting two or more periodontal pathogens (*A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola*) in the saliva of Hispanic and Asian-American individuals compared to Caucasian subjects. On further analysis, however, a more significant factor was related to the length of time the parents of the children had lived in the USA, rather than to ethnicity *per se* (Sirinian et al. 2002) as the salivary detection of these selected periodontal bacteria decreased as the number of years of parental residence in the USA increased. A comparison of the microbiota of twins has shown their subgingival bacterial communities to be more similar in composition than that in unrelated subjects, suggesting some genetic influences (Moore et al. 1993), although these differences can be lost in adulthood (Michalowicz et al. 1999).

Lifestyle, health and age

The frequent intake of food and drink containing fermentable carbohydrates selects for acidogenic and acid-tolerating bacteria in supragingival plaque, which increases the risk of dental caries (Marsh & Martin, 2009). Smoking and diabetes are risk factors for periodontal disease. Smoking may select for potential pathogens such as *T. forsythia*, *Peptostreptococcus micros*, *F. nucleatum* and *Campylobacter rectus* (van Winkelhoff et al. 2001). Smoking cessation can lead to a decrease in the prevalence or proportions of a number of periodontal pathogens, including *Porphyromonas endodontalis*, *Dialister pneumosintes*, *Parvimonas micra*, *Filifactor alocis* and *T. denticola* (Delima et al. 2010). Diabetic patients tend to have a higher frequency of *P. gingivalis*, *A. actinomycetemcomitans*, and *Campylobacter* spp. (Ciantar et al. 2005, Ebersole et al. 2008). The composition of the oral microbiota also changes with age (Percival 2009). This can be as a consequence of a number of host-related events including tooth eruption in early life, hormonal changes or the waning of the immune response in old age. The influence of female hormones in GCF during pregnancy on the prevalence of some periodontal pathogens is controversial (Adriaens et al. 2009), although correlations have been found between maternal hormone levels and *P. gingivalis* and *P. intermedia* (Carrillo-de-Albornoz et al. 2010). There is evidence that the prevalence of some periodontal pathogens is age-related, with *A. actinomycetemcomitans* being more common in younger subjects while *P. gingivalis* was more prevalent with increasing age (Rodenburg et al. 1990, Faveri et al. 2009).

Host defences and host–microbe cross talk

The host has an array of host defences provided by both the innate and adaptive arms of the immune system, the primary

function of which is to protect tissues against microbial colonization and invasion. Indeed, individuals with periodontal disease have hyper-responsive peripheral blood neutrophils (Gemmell et al. 2002, Ryder 2010). A description of the nature of the host defences and their role in periodontal disease is beyond the scope of this review, and the reader is advised to read specialist texts on this broad topic (Gemmell et al. 2002, Devine 2003, Walker 2004, Berglundh & Donati 2005, Ryder 2010). Despite these host defences, the host has evolved over millennia to support a complex resident microbiota and, at first sight, this might appear paradoxical (the ''commensal paradox'') (Henderson & Wilson 1998). It is now apparent that the resident microbiota confers considerable benefit to the host, and that the host is dependent on its microbial residents for its normal development (Wilks 2007). The biological mechanisms that permit this constructive co-existence between the host and the resident microbiota, and yet enable the host to retain the capacity to respond to exogenous microbial insults, are now being dissected, although they are far from fully understood at present. The host is not indifferent to the presence of the diverse microbial communities that reside on its surfaces. It is actively engaged in cross talk with its resident microbiota in order to effectively maintain a constructive relationship. Host cell pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors are strategically deployed in tissues to sample the extracellular and intracellular environments and recognize microbe-associated molecular patterns (MAMPS), such as lipopolysaccharide, lipoteichoic acid, nucleic acid. They activate multiple signalling pathways many of which converge on nuclear factor κB (NF-κB). MAMPs are present on, or are released from, all microbial cells. The host has evolved systems to enable them to tolerate resident microorganisms without initiating a damaging inflammatory response, while also being able to mount an efficient defence against pathogens. Pathogenic and non-pathogenic bacteria may initiate different intra-cellular signalling pathways and innate immune responses in epithelial cells (Canny & McCormick 2008, Hooper 2009, Neish 2009).

The importance of host detection systems in oral tissues is reflected in the fact that abnormal expression of PRRs that bind bacterial lipopolysaccharide (TLR2 and CD14) have been linked to pre-disposition to periodontal disease (Laine et al. 2005, James et al. 2007, Tervonen et al. 2007). Resident oral bacteria determine the normal expression of immune mediators, and resident bacteria in subgingival plaque help to maintain healthy tissue by regulating low levels of expression of intracellular adhesion molecule 1, E-selectin, and IL-8, which in turn can regulate the establishment of a protective layer of neutrophils strategically positioned between the subgingival biofilm and the junctional epithelium (Dixon et al. 2004a, b). Oral commensals and pathogens may activate distinct response pathways in oral epithelial cells (Krisanaprakornkit et al. 2002, Chung & Dale 2004, O'Hara et al. 2006, Hasegawa et al. 2007, Peyret-Lacombe et al. 2009). Certain oral streptococci have been shown to suppress epithelial cell cytokine expression (Hasegawa et al. 2007, Peyret-Lacombe et al. 2009). *Streptococcus salivarius* K12 not only down-regulated epithelial cell inflammatory responses by inhibiting the NF-κB pathway, but also actively stimulated beneficial pathways, including type I and II interferon responses, and exerted significant effects on the cytoskeleton and adhesive properties of the host cell (Cosseau et al. 2008).

There is evidence for host–bacterium cross talk during biofilm development in the gingival crevice. Surface components of subgingival bacteria are involved in adhesion to epithelial cells at the start of colonization and biofilm formation. Fimbriated *P. gingivalis* cells can induce formation of integrin-associated focal adhesions with subsequent remodelling of the actin and tubulin cytoskeleton in primary gingival epithelial cells (Yilmaz et al. 2003). These complex interactions may reflect a possible evolutionary relationship between *P. gingivalis* and host cells, resulting in a balanced association whereby the organism can survive within epithelial cells without causing excessive harm. *P. gingivalis*-mediated disease may result in part from a disruption of this balance by factors that may trigger virulence or lead to host-immune-mediated tissue damage (Yilmaz et al. 2003). The ''commensal communism'' paradigm proposes that our oral microbiota and mucosa form a unified ''tissue'' in which host–microbe ''cross-talk'' is finely balanced to ensure microbial survival and prevent the induction of damaging inflammation (Henderson & Wilson 1998).

The Development of Subgingival Biofilms with the Potential to Cause Periodontal Pathology

This beneficial relation between the host and its oral microbiota can break down. There is a shift in the balance of the subgingival microbiota, with an increase in species richness and diversity, at sites suffering from periodontal disease (Socransky & Haffajee 2005, Marsh & Martin 2009), which become more marked with disease severity. Biofilms from the healthy non-inflamed gingival crevice consist mainly of Gram-positive, saccharolytic, and facultatively anaerobic bacteria, such as *Actinomyces* and *Streptococcus* species, together with low proportions of obligate anaerobes (Slots 1977, Paster et al. 2001). The total number of viable bacteria (microbial load) recovered from the healthy gingival crevice is relatively low. At diseased sites, there is an increase in plaque mass, accompanied by a rise in the proportions of cultivable Gram-negative and obligately anaerobic species, many of which have a proteolytic metabolism. These species are present as characteristic complexes or consortia (Socransky et al. 1998), together with many novel taxa and ''unculturable'' species (Paster et al. 2001, 2006), the majority of which may be Gram positive.

The main theories to explain the origins of these disease-associated microbial species include either exogenous acquisition, translocation from reservoir sites such as the buccal mucosa, or the presence of disease-associated species at healthy sites but in numbers too low to be detected or to be of clinically relevance. By applying microbial ecological principles, a dramatic change to the habitat would be necessary in order for the balance of the microbiota to be shifted to the degree seen in disease. By definition, the putative periodontal pathogens are non-competitive with other members of the resident subgingival microbiota at healthy sites by virtue of their persistence in low numbers. In other ecosystems, such dramatic shifts in microbiota are associated with a major alteration to the habitat, often in terms of changes in nutrient status (e.g. the overgrowth of algae in rivers following the wash-off of nitrogenous fertilizers from neighbour-

ing farm land), pH (e.g. the disruption of aquatic life in lakes by ''acid rain''), or immune status (e.g. reactivation of dormant *Mycobacterium tuberculosis* in the lungs of HIV-infected patients).

Subgingival environmental changes in disease

The host mounts an inflammatory response when plaque is allowed to accumulate beyond levels that are compatible with health, and this can change the local environment to such an extent as to alter the balance of the subgingival microbiota. The host increases the flow of GCF in order to introduce components of the host defences into the crevice. However, GCF also contains an array of complex host molecules including transferrin, haemoglobin, etc. that can be exploited as primary nutrient sources by proteolytic anaerobes with the potential to act as periodontal pathogens (ter Steeg et al. 1987, 1988, ter Steeg & van der Hoeven 1989). For example, organisms such as *P. intermedia* and *P. gingivalis* have an absolute requirement for haemin for growth, and derive this co-factor from the catabolism of host glycoproteins including haemoglobin using cysteine-like proteases such as interpain (Byrne et al. 2009) and gingipains (Dashper et al. 2004), respectively. An increase in haemin availability can dramatically alter the phenotype of bacteria; *P. gingivalis* has increased protease activity, changes the structure of its lipopolysaccharide, and is more virulent when grown under haemin excess conditions (McKee et al 1984, Jain & Darveau 2010).

A further consequence of this proteolytic metabolism is an increase in local pH and a fall in the redox potential which, as discussed earlier, promotes the up-regulation of some of the virulence factors associated with these putative pathogens, and favours their growth at the expense of the species associated with gingival health (i.e. increases the competitiveness of the potential pathogens). If sustained, the combined selective pressures of changed nutrient supply, elevated pH, and lower redox potential will lead to a re-arrangement of community structure and an enrichment of the proportions of the anaerobic and proteolytic component of the microbiota.

Microbial proteolytic activity in the pocket results in cleavage of host defence molecules which can result in an inappropriate inflammatory response causing by-stander damage to the subgingival tissues (O'Brien-Simpson et al 2003, Ryder 2010), thereby providing an even broader range of host molecules for the increasingly metabolically versatile microbial community. Thus, a down-ward spiral can develop in which, if the host fails to control the initial microbial insult, the nature of its response to the subgingival biofilm inadvertently provides conditions that will further select for the pathogens that will subsequently fuel the inflammatory response.

Laboratory studies of microbial responses to changes in host conditions

When plaque was taken from moderately deep pockets (4–7 mm) in patients without symptoms of advanced periodontitis, and was grown in a series of batch culture enrichments on human serum (used to mimic GCF) (ter Steeg et al. 1987), the conditions within the cultures began to change with each step-wise enrichment culture. An initial fall in pH (probably as a result of the removal and metabolism of carbohydrate side-chains from glycoproteins) was followed by a rise in pH as proteins were degraded, and the redox potential fell further over time. Immunoglobulins, haptoglobin, transferrin, and complement C3c were completely degraded. These changes in metabolism were associated with the selection of species associated with periodontal destruction, such as black-pigmented anaerobes, anaerobic streptococci, *Fusobacterium* spp., and spirochaetes; most of these species were not be detectable by culture in the original samples (ter Steeg et al. 1987). As an example, *P. intermedia* could only be detected in one of the three subgingival plaque samples used as an inoculum, and that was $<1\%$ of the total cultivable microbiota. However, after several step-wise enrichments in human serum, *P. intermedia* was detected in the cultures derived from all three clinical samples, and reached peak proportions of 12%, 15%, and 14% of the total culturable microbiota, respectively, within the evolving consortium (ter Steeg et al. 1987). Thus, an organism that was apparently absent, but which must have been present below detectable levels, could become a major component of the microbiota once environmental conditions changed, and novel substrates were introduced. Likewise, in a laboratory culture of ten oral species, the levels of *P. gingivalis* increased from $<5\%$ of the microbiota to levels that dominated the culture when the mucin-based growth medium was supplemented with human serum (to simulate the shift in nutrient supply when GCF flow is increased in periodontal disease). The increased proportions of *P. gingivalis* were accompanied by raised gingipain activity, and an elevation in the culture pH from 6.9 to 7.5 (P. D. Marsh et al., unpublished data), as has been measured in inflamed pockets (Eggert et al. 1991). *P. gingivalis* also outcompeted other black-pigmented anaerobes and rose from $<1\%$ to $>99\%$ of a microbial community when the environmental pH was deliberately shifted from pH 6.75 to 7.50 (Marsh et al. 1993). Collectively, these laboratory data confirm that the composition and metabolic capability of an oral microbial community is responsive to, and can change markedly when the environment (nutrient source, pH, etc.) is altered.

Ecological explanation of subgingival microbial perturbations

The ''ecological plaque hypothesis'' was proposed to describe and explain this dynamic relationship between the host and its resident oral microbiota in health and disease in ecological terms (Marsh 1994, 2003) (Fig. 2). The theory underpinning this hypothesis in the context of periodontal disease is that changes in the environment (a) increase the competitiveness of the putative pathogens (which if present in health, are generally only at low and clinically insignificant levels) at the expense of species associated with oral health, and (b) up-regulate the expression of virulence factors. Importantly, there is acknowledgement of a direct link between local environmental conditions in the host and the activity and composition of the biofilm community. Any change to the host environment will induce a response in the microbiota, and *vice versa*. Implicit in this hypothesis is that although disease can be treated by targeting the putative pathogens directly (e.g. with antimicrobial agents), long-term prevention will only be achieved by interfering with the underlying changes in host environment that drive the deleterious shifts in the microbiota (Marsh 2003). This could be by conventional techniques, such as improving oral hygiene practices to disrupt or remove biofilm and changing

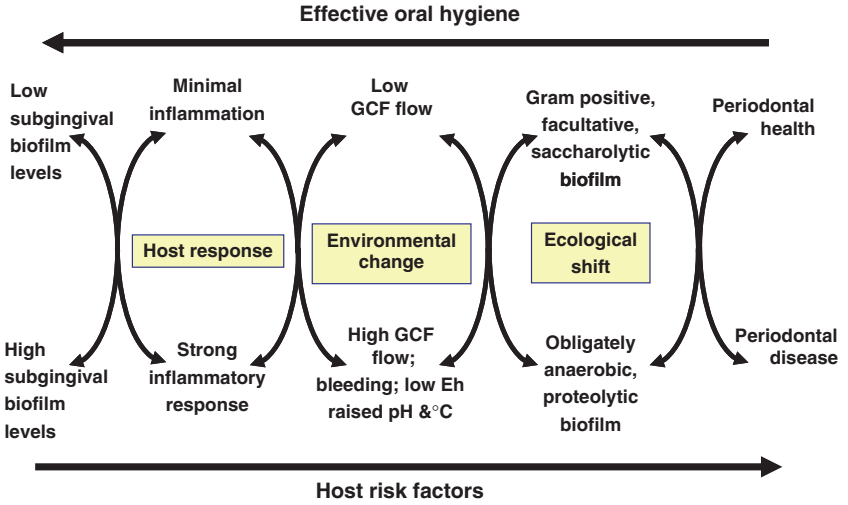

Fig. 2. The ''ecological plaque hypothesis'' in relation to periodontal disease. There is a dynamic relationship between the host environment and the resident subgingival microbiota. An increase in levels of biofilm around the gingival margin leads to a host inflammatory response which, in turn, alters local environmental conditions. These changes will select for a more proteolytic microbial community which will continue to drive the inflammatory response, providing further selection pressures for a proteolytic and anaerobic microbial consortium that is better adapted to the new environment. The changes in microbiota will predispose a site to disease; treatment should remove biofilm but also interfere with the selection pressures driving the deleterious shifts in the subgingival microbiota. Host risk factors (smoking, defects in host defences, etc.) can increase the risk of these deleterious ecological changes in microbiota occurring (Marsh 2003). GCF, gingival crevicular fluid.

life-style (e.g. elimination of risk factors such as smoking). Additionally, more novel approaches could be developed, such as altering the redox potential of the pocket to restrict the growth of the obligate anaerobes (Wilson et al. 1992), or by reducing the severity of the inflammatory response (van Dyke 2008). Novel mediators of inflammation, such as resolvins, are able to pharmacologically manipulate inflammation while facilitating tissue regeneration (Hasturk et al. 2007), and may be a key approach to restrict the nutrient supply for the growth of these deleterious microorganisms while also promoting healing. Indeed, in the ecological plaque hypothesis, it is accepted that disease will inevitably re-occur unless the underlying pre-disposing factors that are driving these deleterious shifts in microbiota are addressed (Fig. 2).

Concluding Remarks

The host environment directly influences the development, composition and metabolic activity of the resident oral microbiota. In health, the oral microbiota is in dynamic equilibrium with the host, but a substantive change in a key parameter that influences microbial growth can perturb this equilibrium and determine whether the microbiota will have a commensal or pathogenic relationship with the host at a site. An understanding of these host–microbe inter-relationships is fundamental to developing effective treatment strategies.

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Clinical Relevance

Scientific rationale for the study: A review of the scientific literature suggests that there is a direct relationship between the properties of the host and the composition and activity of the resident microbiota. The resident oral microbiota provides benefits to, and is essential for the normal development of the host. However, many of the biological changes associated with the development of periodontal disease perturb this beneficial relationship and select for an increasingly proteolytic and pro-inflammatory subgingival microbiota.

Principal findings: Changes to the subgingival environment can affect bacterial gene expression (including the production of virulence factors) and increase the competitiveness of putative periodontal pathogens. The resultant changes in biofilm composition and activity can predispose a site to disease.

Practical implications: To effectively control periodontal disease, treatment must also deal with the underlying factors that are responsible for driving the deleterious shifts in the subgingival microbiota.