Microbiologic Specificity of Periodontal Diseases

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Traditional Nonspecific Plaque Hypothesis (NSPH) (Loesche in 1900):

The nonspecific plaque hypothesis maintains that periodontal toxic products by the entire plaque flora are proportional to the severity of the gingival inflammation. According to this thinking, when only small amounts of plaque are present, the harmful products are neutralized by the host. Similarly, large amounts of plaque would produce large amounts of toxic products, which would essentially overcome the host's defenses. The NSPH has focused on the quantity of plaque that determined the pathogenicity without discriminating between the levels of virulence of bacteria. Believing this, the host would have a threshold capacity to detoxify bacterial products (e.g., saliva neutralizing acid) and disease would only develop if this threshold was exceeded and the virulence factors could no longer be neutralized.

The conclusion was that if any plaque has an equal potential to cause disease, the best way of disease prevention would be nonspecific mechanical removal of as much plaque as possible by e.g., tooth brushing or tooth picking.

Several observations contradicted these conclusions. First, some individuals with considerable amounts of plaque and calculus, as well as gingivitis, never developed destructive periodontitis.

Second, individuals who did present with periodontitis demonstrated considerable sitespecificity in the pattern of disease. Some sites were unaffected, whereas advanced disease was found in adjacent sites.

Third, the improvement of techniques to isolate and identify bacteria in the mid-20th century led to the abandoning of the NSPH.

Although the nonspecific plaque hypothesis has been discarded in favour of the specific plaque hypothesis or the ecologic plaque hypothesis, much clinical treatment is still based on the nonspecific plaque hypothesis through mechanical plaque removal, representing the most efficient way of preventing disease.

Specific Plaque Hypothesis (Loesche in 1976):

The specific plaque hypothesis states that only certain plaque is pathogenic, and its pathogenicity depends on the presence of or increase in specific microorganisms. This concept predicts that plaque harbouring specific bacterial pathogens results in periodontal disease because these organisms produce substances that mediate the destruction of host tissues. Acceptance of the specific plaque hypothesis was encouraged by the recognition of A. actinomycetemcomitans as a pathogen in localized aggressive periodontitis.

The SPH in periodontal diseases were proposed to be inflammations caused by specific periopathogens and antibiotic treatment would be effective. *However certain limitations are associated with this hypothesis:*

1. Clinical studies evaluating the effectiveness of antibiotics as adjuncts in periodontal therapy stated that the disease is reversible and retained after stopping antibiotic therapy.

2. Long-term use of antibiotics led to bacterial resistance. Additionally, the use of chlorhexidine after scaling and root planing in patients with periodontitis had only an uncertain positive effect and concluded that the extensive use of chlorhexidine may be questioned.

3. potential periopathogens included: protozoa, spirochetes, streptococci, and actinomyces. In addition, Gram-negative, anaerobic rods including black pigmented Prevotela melaninogenica and Campylobacter and facultative anaerobic, were identified as periopathogens. However, these findings were limited due to the large number of uncultivable species (~50%) and the biastoward easily cultivable species. The finding of different species related to periodontal disease led to the idea that oral disease could be initiated by several specific pathogens.

Updated Nonspecific Plaque Hypothesis (Theilade, 1986):

The "specific pathogens" from the SPH were indigenous bacteria and sometimes common bacteria in health, which led to an updated NSPH. The updated NSPH took into consideration that the overall activity of microbes could lead to disease through differences in the virulence factor of the bacteria in dental plaque. The hypothesis stated that all bacteria in plaque contribute to the virulence of the microflora by having a role in either colonization, evasion of the defence mechanism, and/or provocation of inflammation and tissue destruction.

Reports have been stated that "any microbial colonization of sufficient quantity in the gingival crevice causes at least gingivitis" was supported by the fact that a non-pathogenic plaque (i.e., not causing gingivitis in the absence of oral hygiene) had never been observed. Additionally, it was considered that some people have gingivitis for a lifetime without tissue and bone destruction, while others encounter rapid progression into periodontitis. Unlike the classic NSPH, the updated NSPH could explain this by taking into account that differences in the plaque microbial composition could lead to differences in pathogenic potential.

Ecologic Plaque Hypothesis (Marsh 1994):

"Ecological Plaque Hypothesis" (EPH), the disease is the result of an imbalance in the total microflora due to ecological stress, resulting in an enrichment of some "oral pathogens" or disease-related microorganisms. This idea was not entirely new since the review proposing the U-NSPH concluded that "increased virulence of plaque (leading to disease) is due to a plaque ecology unfavourable to the host and favourable for overgrowth by some of the indigenous bacteria having a pathogenic potential".

Importantly, the changes in microbial composition lead to changes in ecological factors such as the presence of nutrients and essential cofactors, pH and redox potential. It is still generally accepted that the composition of dental plaque depends on the environment. As well as considering the reverse: the bacteria in dental plaque affect the environment. For instance, early

colonizers of supragingival dental surfaces, are usually facultative anaerobic bacteria that use oxygen, producing carbon dioxide and hydrogen. This lowers the redox potential giving strict anaerobes a chance to settle and multiply in the biofilm. Bacterial growth is dictated by the environment, which in turn is influenced by bacterial metabolism, leading to mutual dependencies in health but also a chain of events that lead to diseases. The importance of the host-dependent environment in the selection of bacterial species that colonize should not be neglected.

However, like the other hypotheses, the traditional EPH does not address the role of genetic factors of the host that significantly contribute to the composition of dental plaque and susceptibility to disease.

Keystone Pathogen Hypothesis (Hajishengallis et al., 2012):

The concept of keystone species is derived from basic ecological studies. Certain species have an effect on their environment that is disproportional relative to their overall abundance. “The Keystone-Pathogen Hypothesis” (KPH) indicates that certain low-abundance microbial pathogens can cause inflammatory disease by increasing the quantity of the normal microbiota and by changing its composition.

The identification of keystone pathogens would have significant clinical benefits as

1. It could facilitate the development of novel treatments for polymicrobial or complex dysbiotic diseases by focusing therapeutic strategies on only a limited number of bacterial targets that stabilize the dysbiotic microbial community.

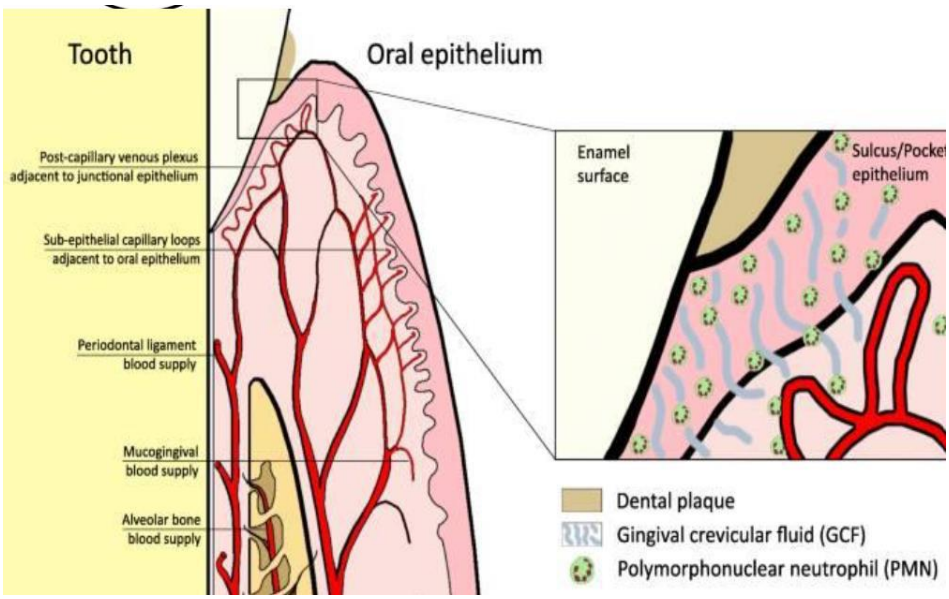
2. Moreover, novel, targeted diagnostic tools could be developed if a complex polymicrobial disease is shown to be driven by a keystone pathogen or by a limited number of microorganisms acting in this manner.

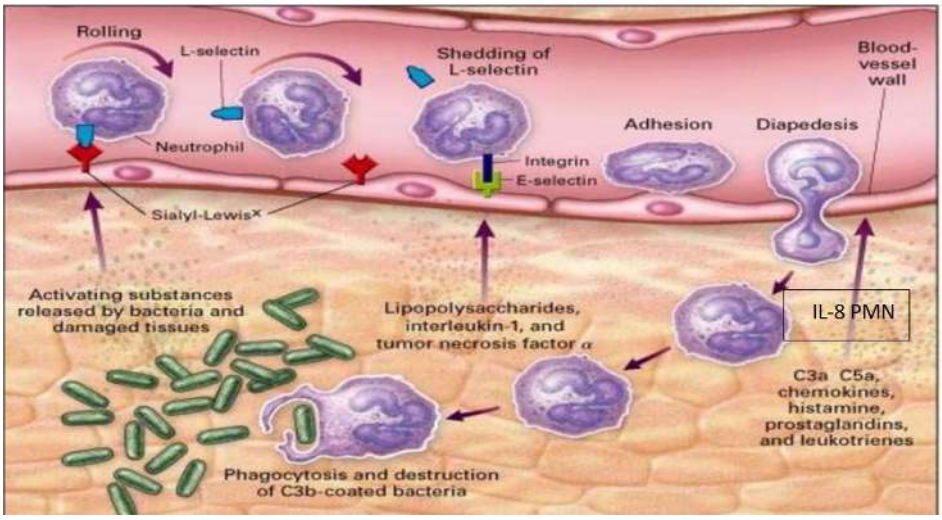
For instance, Porphyromonas gingivalis is shown to be able to manipulate the innate immune system of the host. By doing so it was hypothesized that it does not only facilitate its survival and multiplication, but of the entire microbial community. In contrast to dominant species that can influence inflammation by their abundant presence, keystone pathogens can trigger inflammation when they are present in low numbers. When the disease develops and advanced stages are reached, the keystone pathogen is detected in higher numbers. Importantly, even though their absolute number increases, keystone pathogens can decrease in levels compared to the total bacterial load which increases as plaque accumulates in periodontitis.

The KPH was developed by observing the properties of the “red complex” bacterium P. gingivalis. The role of the host immune system is critical in the KPH. At health, periodontal tissue contains a wall of neutrophils, between the plaque and the epithelial surface, residing just outside the epithelial cells. Expression of mediators such as interleukin 8 (IL-8), intercellular adhesion molecule (ICAM) and E-selectin is required to form this neutrophil wall. E-selectin is

required for neutrophil migration from the highly vascularized gingival tissue, IL-8 is a key neutrophil chemo-attractant produced by epithelial cells, and ICAM facilitates the adhesion of neutrophils to the tissue allowing the formation of this wall.

Furthermore, the epithelium expresses low levels of a wide range of toll-like receptors (TLRs), including TLR1-TLR9 that mediate the response to a broad range of microorganisms.





Evidence was found of three major KPH mechanisms of P. gingivalis that could impair the above-mentioned host defences:

(1) Toll-like receptor (TLR) response manipulation

(2) Interleukin 8 (IL-8) subversion

(3) The corruption of the complement system.

The TLR response: is manipulated by P. gingivalis with the help of two types of lipopolysaccharides (LPS) (type I) and (type II). Type I is a TLR4 agonist thus activating the immune system, while Type II is a TLR4 antagonist inhibiting the immune response to P. gingivalis. The concentration of iron determines which type of LPS is expressed. In the oral cavity, the main source of iron is hemin, found in the gingival crevicular fluid (GCF). During the inflammatory process, GCF increases stimulating P. gingivalis type II LPS expression, thus reducing the TLR4 response. It was proposed that this could facilitate survival and multiplication of the entire microbial community.

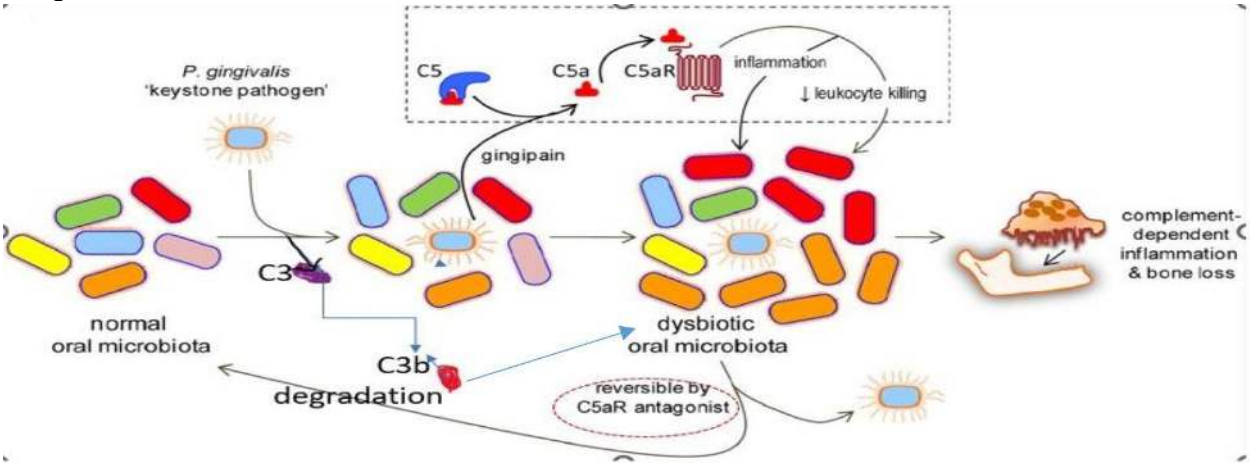
IL-8 response: Porphyromonas gingivalis can block the production of IL-8, which is produced by gingival epithelial cells in response to other bacteria, by secreting a serine phosphatase that inhibits the synthesis of IL-8. This process is called "local chemokine paralysis" and delays the recruitment of neutrophils preventing proper neutrophil wall formation, of which was proposed that it could facilitate initial microbial colonization of the periodontium.

Other "red complex" bacteria such as T. denticola, are also able to manipulate the IL-8 response of the host however the mechanism(s) involved is not understood.

Complement system response: The third and best in vivo documented keystone pathogen mechanism is the interference with the complement system. The complement system is a major component of the innate immune response involved in recognizing and destroying microorganisms with complex roles in homeostasis and disease. To be a successful pathogen in humans, a microorganism must avoid complement-mediated detection and killing.

Again, the best-studied example in the oral cavity is P. gingivalis that produces membrane-bound and soluble proteinases called "gingipains". Gingipains can cleave complement factors C3 and C5 into active fragments C5a (cell activator) and C3b (phagocytosis enhancer). These fragments can be further degraded by gingipains resulting in loss of their function. As well as this leads to an increased activation of the C5a receptor (C5aR) on leukocytes. C5aR is involved in cross-talk with TLR2, which is activated in parallel by P. gingivalis (and other bacterial) surface ligands. While this crosstalk leads to increased inflammation, it impairs the killing capacity of leukocytes, this mechanism has a major role in accelerating periodontitis development and bone loss. A P. gingivalis strain that lacks gingipains failed to change the oral microbiota and induce bone loss. Additionally, periodontitis did not develop in mice lacking one of the two involved receptors C5aR or TLR2.

This provides clear evidence that in mice the dysbiosis caused by P. gingivalis is mainly due to ***complement subversion.***



P. gingivalis failed to cause dysbiosis and periodontitis if :

• Absence of commensal microbiota.

• The host lacked the cellular receptors necessary to subvert leukocyte defences.

• The bacterium lacked a crucial enzymatic activity involved in leukocyte subversion. In conclusion, it was proposed that currently known and unknown keystone pathogens use a combination of these and presently unknown mechanisms to manipulate the innate defence system leading to destructive periodontitis.

